



# ANNALS of SURGERY

A MONTHLY REVIEW OF SURGICAL SCIENCE AND PRACTICE  
ALSO THE OFFICIAL PUBLICATION OF THE AMERICAN SURGICAL  
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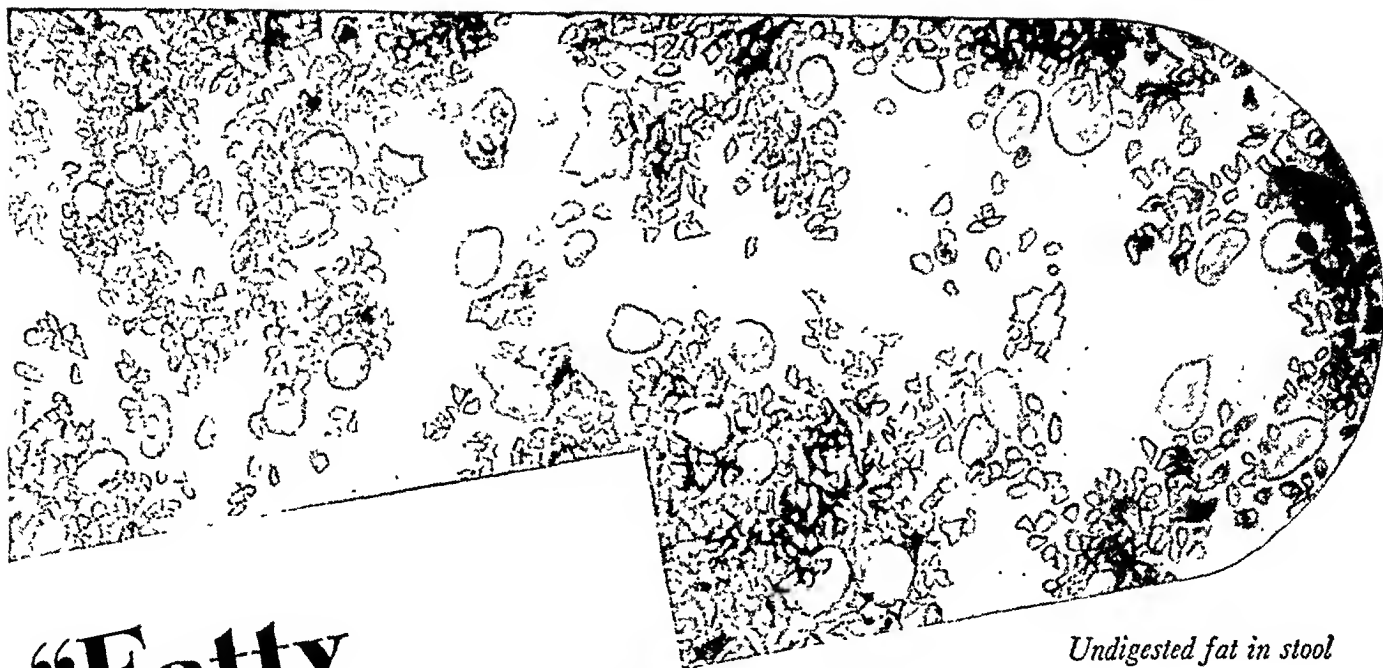


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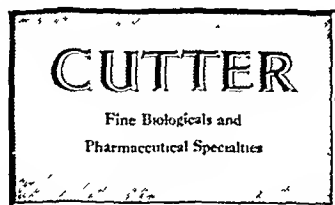
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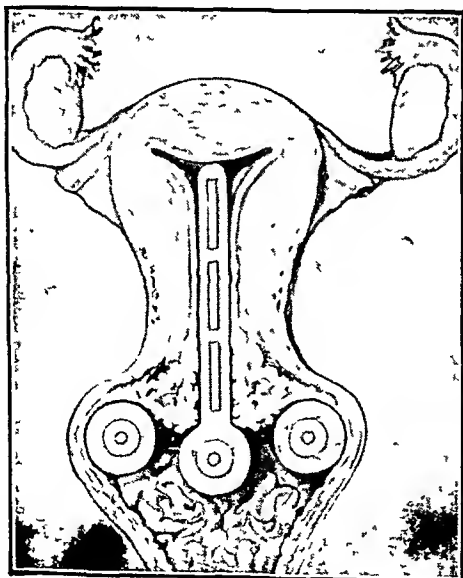
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# ANNALS OF SURGERY

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## ANNOUNCEMENT



THE EDITORIAL BOARD and the Publishers take pleasure in welcoming two new members to the Editorial Board of the ANNALS OF SURGERY:

Dr. Robert M. Janes, *Professor of Surgery, University of Toronto, Toronto, Canada.*

Dr. Henry N. Harkins, *Professor of Surgery, University of Washington, School of Medicine, Seattle, Washington.*

Dr. Janes will represent Canadian surgery on the Editorial Board, filling the vacancy created by the death of Dr. Roscoe Graham. Dr. Harkins, who is Editor-in-Chief of the *Quarterly Review of Surgery*, will make an able representative from the Pacific coast.

The addition of these two surgeons brings the number on the Editorial Board to the former figure of twelve. The Publishers and the Editorial Board extend a hearty welcome to these two new members, who will help carry on the high standards of excellence of the ANNALS OF SURGERY.

—JOHN H. GIBBON, JR., M.D.

### NOTICE TO SUBSCRIBERS

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Delays in the appearance of this and other recent issues of the ANNALS OF SURGERY have been due to present unsettled conditions in the printing trades. A return to original schedules is expected as soon as a settlement of these difficulties is reached.

These conditions will also involve delays in the production of reprints.

## RESULTS FOLLOWING SUBTOTAL GASTRECTOMY FOR DUODENAL AND GASTRIC ULCER \*

FORDYCE B. ST. JOHN, M.D., HAROLD D. HARVEY, M.D., JOSE M. FERRER, M.D.  
AND R. W. SENGSTAKEN, M.D.

NEW YORK CITY

FROM THE DEPARTMENT OF SURGERY, COLUMBIA UNIVERSITY, COLLEGE OF PHYSICIANS AND SURGEONS, AND  
THE SURGICAL SERVICE OF THE PRESBYTERIAN HOSPITAL IN THE CITY OF NEW YORK

DURING THE DECADE 1936 TO 1945, inclusive, 394 partial gastric resections were performed for peptic ulcer at the Presbyterian Hospital in New York City. In view of the current discussion of the relative virtues of vagus nerve resection and gastric resection, a review of these cases is reported at this time. The cases reviewed include both ward and private. They were operated on by all members of the general surgical staff and in about a quarter of the instances by the surgical residents, usually assisted by a staff member. The results are therefore not to be attributed to the skill of a specialist in this field of surgery, but are those obtained in a teaching institution.

### OPERATIVE TECHNIC

In most instances, a Polya type of resection was done, the jejunal loop for anastomosis being brought up anterior to the colon more often than posterior. Recently, the Hofmeister procedure with a short posterior loop has been carried out most frequently. It has not been possible to show any consistent difference in the early or late results of the Polya type of resection whether the anterior or posterior type of anastomosis was done or whether the ulcer was removed, cut through or left in. In some instances when a duodenal ulcer was left in, the pylorus and even part of the antrum were left in as well, but the mucosa was removed. These cases have done as well as the rest. In the Polya types of resection it has seemed to make no difference whether the anastomosis was done isoperistaltic or antiperistaltic. It has been our impression that there are less immediate postoperative difficulties after the Hofmeister type of resection than after the Polya type, as has been noted in other clinics. We have not yet had an opportunity to compare the late postoperative results following these two procedures, but it appears that the Hofmeister type will do at least as well. An effort has been made in nearly every resection, whatever the type, to remove two-thirds or more of the stomach, so that this series differs from older ones which included pylorotomies. No occlusion procedures leaving in the mucosa were done, and no two-stage procedures. In a few instances, a jejunojejunostomy was tried, uniting the afferent and efferent jejunal loops in a manner similar to a Finney pyloroplasty.

The cases subjected to resection were, in general, the ones whose symptoms were severe. No standard criteria are set up in the hospital to determine when operation should be done, but the indications usually are either suspicion

\* Submitted for publication, January 1948.



of carcinoma or chronicity of symptoms indicating failure of medical treatment to control pain, repeated hemorrhages or persistent obstruction. This report does not include cases which were operated on as emergencies for perforation or bleeding, nor does it include cases where a previous gastro-enterostomy was taken down at the time of the resection, although the last complication has added nothing to the postoperative death rate or subsequent recurrence of symptoms.

#### METHOD OF POSTOPERATIVE ANALYSIS

The chief value of the report lies, we believe, in the completeness of the record of what has happened to the patients after they have left the hospital. This is the result of the efficiency of the Follow-Up Clinic which has been administered now for thirty years by Miss Retta Pinney. For many years the two senior authors have spent two full and busy mornings each fortnight

TABLE I.—*Partial Gastrectomy for Ulcer*

Number of Cases Being Followed

Currently followed, i.e. seen or heard from in 1945 or 1946.....	344	87.3%
Died in hospital or after from any cause.....	37	9.4%
Lost to follow-up .....	13	3.3%
	<hr/>	<hr/>
	394	100.0%

Of the lost cases all but three had been followed for at least one year.

Of the currently followed cases about 90% had been personally interviewed in 1945 or 1946; the remainder heard from by letter.

TABLE II.—*Partial Gastrectomy for Ulcer. Follow-up Results*

Group		Number of Patients
4 .....	271	
3 .....	65	
	<hr/>	
Total of Satisfactory Cases.....		336
2 .....	17	
1 .....	20	
	<hr/>	
Total of Unsatisfactory Cases.....		37
Insufficient Data .....		3
Postoperative Deaths .....		18
		<hr/>
Total .....		394

in this Clinic, interviewing and examining patients who have had gastric operations. We estimate that over 80% of the follow-up records are based on personal interview either in this Clinic or in private practice, the remainder being the result of communication with patients who cannot be reached for interview. There is no substitute for the personal interview as a means of finding out what the patient's state of health is. The status of the 394 patients on July 1, 1946, with a few subsequent corrections, was as shown in Table I.

Each time a patient is seen or heard from, he is rated as to his follow-up status on an anatomic, symptomatic and economic basis. This report has to do only with the symptomatic rating. The symptoms considered are those which seem to be related to his ulcer or his operation. A scale of four is used. A rating of four means no symptoms; a rating of three means mild complaints, but hardly beyond the range which a well person might have. Ratings of four

## SUBTOTAL GASTRECTOMY FOR ULCER

TABLE III.—*Partial Gastrectomy for Ulcer. Unsatisfactory Cases*

1. *Cases Unsatisfactory Because of Symptoms Suggesting Persistent Ulcer:*
  - a. Proved jejunal ulcer:
    - 703298 K. Perforated jejunal ulcer 2½ years after resection.
    - 701898 N. Jejunal ulcer 2 years after resection. Died as a result of operation on this ulcer.
  - b. Persistent pain or bleeding. Possible jejunal ulcer:
    - 689322 F. Report once suggested recurrent ulcer. Not seen at follow-up since 1942. Now reports he is symptom free.
    - 761845 G. Tarry stools four days with pain, 2½ years after resection. Smoking too much. Roentgen-ray showed possible ulcer of efferent loop. Now symptom free.
    - 777565 D. Three episodes of bleeding in 8 years. Roentgen-ray once suggested a jejunal ulcer. Small resection.
  - c. Bleeding, otherwise symptomless:
    - 813904 M. Episodes of tarry stools. No other symptoms. Source of bleeding not found. Roentgen-ray showed no lesion.
  - d. Gastro-intestinal symptoms suggesting ulcer syndrome, but no ulcer demonstrable and no bleeding:
    - 665392 P. Generally much better than before operation. State of well-being varies from day to day. Nervousness, irritability, despondency, some pain and occasional vomiting.
    - 565880 S. For 5 years, fullness and gaseous distress after meals, empty feeling between meals, dizziness, some loss of weight. Now no digestive complaints, but lack of energy and strength.
    - 580765 G. Persistent vomiting immediately after leaving hospital, but last letter stated she felt much better. Lives in South Africa. Lost to follow-up at 6 months.
    - 749020 K. Many complaints after operation, only 2 of which were directly gastro-intestinal in nature. Seemed psychoneurotic. Anxious to prove poor health will not permit him to be deported to Central America whence he came. Jejuno-plastic operation.
2. *Cases Unsatisfactory Because of Effects of Operation:*
  - a. Late Infection or obstruction:
    - 680254 L. Adhesions distal to stoma causing partial ileus, not wholly relieved by three operations. Jejuno-plastic operation.
    - 561763 B. Died 6 months after resection with esophageal stricture and subphrenic abscess from duodenal fistula.
    - 242616 C. Died following second operation which was done for intussusception near stoma. Originally gastric ulcer.
    - 416007 W. Died following second operation done for obstruction of afferent loop. Originally gastric ulcer.
    - 603964 O. Died following second operation. Afferent loop leading to lesser curvature had become constricted behind mesentery of efferent loop, causing ileus, gangrene, peritonitis.
  - b. Late hemorrhage:
    - 517123 H. Died following second operation to check a severe hemorrhage from superior pancreatico-duodenal vessels, 23 days after resection.
  - c. Pulmonary tuberculosis, activated by operation:
    - 657949 W. Developed active tuberculosis while in hospital after operation. Dead in 6 months. Originally gastric ulcer.
  - d. Spinal cord damage from spinal anesthesia:
    - 703328 K. Incapacitated as result of spinal cord damage.
3. *Unsatisfactory for Miscellaneous Reasons:*
  - a. Digestive symptoms probably not caused by ulcer:
    - 820454 McM. Repeated brief episodes of abdominal pain, nausea and vomiting. Has regional ileitis.
    - 605468 S. Chronic invalid. Psychoneurotic. Persistent malnutrition. Roentgen-ray showed no lesion except slow emptying of gastric pouch, after operation.
    - 502188 B. Symptoms of intestinal obstruction on two occasions after operation. Hard to say whether ulcer recurrence played a part. Jejuno-plastic operation.
    - 740173 K. Persistent epigastric symptoms. No explanation found by roentgen-ray. No ulcer found at operation. Symptoms after operation similar to those before, but less frequent, and no bleeding.

TABLE III (Continued)

- b. Bleeding shortly after operation, then satisfactory:
  - 559888 P. Bled shortly after operation. Now over two years symptom free.
  - 547353 G. Hematemesis one month after operation. No subsequent bleeding for three years.
- c. Unsatisfactory after operation; now symptom free but follow-up is short:
  - 786292 D. Occasional vomiting while smoking heavily four months after operation. Symptom free since, for one year.
  - 767851 S. Unsatisfactory first 6 months. Too early to rate finally. No symptoms now. Duodenal and gastric ulcer.
- d. Secondary operation needed. Symptom free thereafter:
  - 593806 H. Division of peritoneal bands nearly five years after operation.
  - 568974 B. Entero-enterostomy necessary for dilated gastric loop. Five years since, symptom free. Originally gastric ulcer.
  - 660994 L. Division of adhesions two years after operation.
  - 567938 M. Efferent loop blocked by adhesions, requiring second operation.
  - 620990 R. Adhesions remote from original operation in left lower quadrant. Originally gastric ulcer.
  - 675259 A. Entero-enterostomy six weeks after operation.
  - 675436 E. Wound infection, septicemia, abscess of kidney. Hemolytic staphylococcus aureus, requiring two hospitalizations with operation. No important gastric symptoms.
  - 741120 S. Postoperative hernia requiring repair.
  - 423620 E. Infected sinuses in wound requiring two operations.
- e. Secondary operation needed. Short follow-up:
  - 791509 M. Two operations for intestinal kinks and a new anastomosis made at a third. Too soon to appraise final results.
- f. Gastric carcinoma, perhaps present at operation for ulcer above site of resection:
  - 481379 C. Bleeding continued after operation, beginning less than one year after resection. Carcinoma of fundus resected three years after resection for ulcer. Died.

and three are considered satisfactory. Two and one indicate unsatisfactory ratings. In the great majority of instances there is no difficulty in giving a rating. At times questions arise, particularly in neurotic patients, of whether complaints are severe enough to warrant an unsatisfactory rating or whether or not they are related to the ulcer syndrome or to the operation. The effects of worry, tension and indiscretions in eating and drinking present themselves at times for consideration. It is easy, for instance, to say that a patient crippled with arthritis is still satisfactory from the standpoint of ulcer therapy, but conditions such as ileitis or diverticulitis or psychoneurosis may give rise to confusion. In such cases, one can only use one's best and honest judgment, recalling that the object of the rating system is to find out the truth and not to promote or condemn any form of therapy which has been employed.

This method of rating leads to some incongruous results. Several patients who say they are much improved since the operation are nevertheless rated as unsatisfactory. On the other hand, a few patients have been called satisfactory in spite of the fact that they may vomit at times or cannot gain as much weight as they want. It is our experience that the group who do not at first gain weight may gain after a year or two, although some patients never do but are well and working. Especially during the first year, patients may vomit from overloading their stomachs with meals which would not disturb a normal person. Unless this symptom were pronounced we would not consider that it rendered them unsatisfactory but would place them in Group 3. There

are a few people who complain of sweating and weakness after eating, the so-called “dumping syndrome,” but, if these symptoms are not severe, they are similarly regarded. This is an interesting phenomenon, as yet unexplained.

TABLE IV.—*Partial Gastrectomy for Ulcer. Postoperative Complications*

No complications .....	161
Pneumonia .....	92
Atelectasis .....	13
Pulmonary embolus .....	4
Pulmonary infaret .....	5
Spasm or obstruction of efferent loop.....	12
Spasm or obstruction of afferent loop.....	2
Excessive vomiting .....	32
Slow gastric emptying .....	3
Biliary fistula .....	24
Pancreatic fistula .....	2
Gastrointestinal hemorrhage .....	9
Hemorrhage from other source..	3
Diarrhea .....	11
Severe amigen reactions .....	8
Other infusion reactions.....	3
Shock .....	2
Wound infection .....	14
Infection of drainage tract.....	8
Disruption .....	5
Urinary retention .....	15
Headache .....	4
Meningismus .....	2
Unexplained fever .....	12
Phlebitis .....	5
Auricular fibrillation .....	3
Distension .....	5
Parotitis .....	4
Pancreatitis .....	4
Jaundice .....	3
Cerebral accident .....	2
Cardiac failure .....	1
Coronary occlusion .....	1
Paroxysmal tachycardia .....	1
Other tachycardia, unexplained .....	1
Psychosis .....	1
Convulsion .....	1
Transfusion reaction with uremia.....	1
Asphyxia (blood in trachea).....	1
Upper respiratory infection .....	3
Pelvic abscess .....	1
Gangrene of colon .....	1
Gangrene of jejunum .....	1
Massive pulmonary collapse .....	1
Massive pleural effusion .....	1
Acute pulmonary TBC .....	1
NOTE: Incidence of acute diffuse peritonitis and peritoneal abscess difficult to determine.	

POSTOPERATIVE RESULTS

Over the years, as the follow-up visits multiply, a record emerges of the patient's state of well-being since the operation. In Table II is given a summary of the results. In this Table the patients are grouped according to the lowest rating to which they fell during their follow-up course, with the exception that ratings during the first postoperative year, while the patient is becoming adjusted to his new digestive mechanism, are sometimes disregarded. To

achieve a Group 4 rating a patient must never have fallen below a four after his first year; a single drop to Group 3 or Group 2, for instance, would place him in that lower group.

TABLE V.—*Partial Gastrectomy for Ulcer. Postoperative Deaths*

Chart No.	Age	Carcinoma Suspect	Day Post-op	Autopsy	Apparent Causes of Death
369171	60	No	4	Yes	Pneumonia.
444085	60	No	8	No	Pneumonia. Leaking duodenal stump. Peritonitis.
564823	58	No	6	Yes	Gangrene of jejunum following occlusion of superior mesenteric artery due to arteriosclerosis of aorta.
588457	48	Yes	5	Yes	Gangrene of transverse colon.
557952	60	Yes	1	Yes	Massive collapse of lungs. Had Stokes-Adams syndrome.
544719	62	Yes	7	No	Atelectasis, auricular fibrillation, pulmonary embolus.
645412	30	No	7	No	Bile peritonitis, probably from leaking duodenal stump.
630929	63	Yes	11	No	Cerebral vascular accident.
699731	61	Yes	12	Yes	Disorientation, pneumonia, incontinence, decubiti, hypoproteinemia, coma, heart failure, subhepatic abscess from leaking duodenal stump.
728277	50	No	17	Yes	Pneumonia, leaking duodenal stump with abscess, severe distention (not mechanical), diffuse peritonitis, pancreatic fat necrosis, hiccough, jaundice. Irrational.
601089	50	No	16	No	Pulmonary embolus.
733712	64	No	11	Yes	Transfusion effect probably. Uremia, jaundice, hiccough, pneumonia.
752813	65	Yes	2	No	Long operation. Shock, coronary occlusion.
751735	43	Poss.	8	No	Bronchopneumonia, distention, disruption with evisceration, inhaled vomitus during closure of disruption, fatal pneumonia.
772174	52	Yes	6	Yes	Hypertensive 220/120. Mild heart failure. Biliary fistula. Cause of death uncertain.
783912	49	No	30	No	Pneumonia, delirium, subhepatic abscess from leaking duodenal stump, hemorrhage into abscess, jejunostomy feedings.
797516	73	Yes	5	Yes	Pulmonary embolus, infarct of lung, pneumonia. Thrombus in right femoral vein.
801055	48	No	44	No	Spinal anesthesia. Acute meningitis beginning 15th day after operation.

As appears in Table II, by our standards 336 patients have never been unsatisfactory since their operation. This number is 85% of all the patients who underwent resection, or 90% of all the patients followed (disregarding the postoperative deaths and the three not followed). An encouraging fact is that no case which went for five years without becoming unsatisfactory thereafter fell into an unsatisfactory group. This is in striking contrast to the record following posterior gastro-enterostomy, in which each year brought new failures. In this series, 99 persons were followed for five years, of whom 12% became unsatisfactory, while of the larger number followed for less than five years, 9% became unsatisfactory. The difference is not significant.

SUBTOTAL GASTRECTOMY FOR ULCER

ANALYSIS OF UNSATISFACTORY CASES

Of the cases rated as unsatisfactory in Table II, some should not be so regarded without qualification. Two groups stand out as clearly unsatisfactory, viz., those who had symptoms suggesting persistent ulcer and those who had uncorrected harmful effects from the operation. The remainder of the cases called unsatisfactory are so rated because they have to be differentiated from the group that was consistently satisfactory, but they cannot be said to have been treated unsuccessfully from the standpoint of their ulcers. Table III elaborates these statements.

Table III contains several facts of interest. It shows that the incidence of proven jejunal or marginal ulcer has been two out of 373 cases that survived operation and were followed. In three others, jejunal ulcer may have occurred. In no other case has its presence been seriously suspected. The incidence has been, therefore, somewhere between 0.5% and 1.4%. The number of patients whose symptoms suggested persistent ulcer syndrome is 10, about 2.7%. There were eight whose difficulties stemmed from the operation or the anesthesia, of whom six died. These will be mentioned later when the postoperative deaths are discussed. There are four who have digestive complaints which do

TABLE VI.—*Partial Gastrectomy for Ulcer*. Chief Causes of Postoperative Deaths  
The causes of death often were multiple, but the apparent chief causes can be grouped as follows:

Duodenal stump complications.....	4
Pneumonia .....	3
Pulmonary emboli .....	3
Massive collapse of lung.....	1
Transfusion effect .....	1
Gangrene of transverse colon.....	1
Thrombosis of superior mesenteric artery.....	1
Cerebral accident .....	1
Coronary occlusion .....	1
Meningitis .....	1
Uncertain .....	1

Duodenal stump complications were a secondary cause of death in 2 of the above cases; pneumonia of serious degree in 3.

not seem to be a continuation of the ulcer syndrome, 14. who had transient difficulties not apparently due to ulcer, and one who died of gastric carcinoma which might have been present at operation. It is a matter of opinion how to consider the last-named groups, which total 19, when appraising the success of the operation as a means of treating ulcer. It may be leaning over backwards to rate them as unsatisfactory. Another interesting fact which does not show in the table is that every case that had persistent digestive symptoms after operation had a duodenal ulcer before; no gastric ulcer gave symptoms after operation except such as could be attributed to the operation itself. The patients listed in the table had duodenal ulcers unless otherwise recorded.

POSTOPERATIVE COMPLICATIONS IN HOSPITAL

Table IV gives the incidence of postoperative complications that occurred while the patients were in the hospital, as they are recorded on the charts. The list is probably not wholly accurate but gives an approximate picture of

the important difficulties. The recorded incidence of atelectasis is probably far too low. The cases grouped under this heading are those with signs of atelectasis but with clinically minimal accompanying pneumonia. Most of the pneumonias we believe started with atelectasis but this does not appear in the table. One hundred sixty-one patients got well without complications. The pulmonary complications were the most frequent. Next came persistent vomiting, which in some instances was attributable to spasm or obstruction of the efferent jejunal loop. The high incidence of biliary fistulae may be due to the fact that in most of the cases a drain was placed down to the region of the duodenal stump. We adopted the practice of draining the region of the duodenal stump because we had found that in the previous decade the chief cause of our postoperative fatalities had been leakage from the stump. Drainage has not fully solved the problem. In spite of drainage, there have been fatalities due chiefly to duodenal stump leakage, although the deaths from this cause have been fewer in number since drainage was adopted. Certainly the bile fistulae have occurred too frequently but most of them have been little more than an annoyance and, in patients who survived, all have healed spontaneously, usually within two weeks. It may be that with the Hofmeister type of procedure there will be fewer cases of back pressure in the duodenum, which we have believed to be one of the causes of fistulae developing in the past. It may be possible also to learn to recognize which stumps are insecurely closed and should therefore be drained in a manner that can take care of anticipated profuse leakage. We realize that there are clinics whose recorded death rate is lower than ours, in which drainage is rarely employed.

#### POSTOPERATIVE DEATHS

The list of postoperative deaths is set forth in Table V. The first item of note is the age of the patients that died. Of the 18 deaths, 16 occurred in patients over age 45, and 13 in patients over age 50. The postoperative mortality among patients under age 45 was about 1%; over this age it was 7.6%. These figures emphasize the safety of the operation in the relatively young and the need for caution and careful study before recommending resection in people of more advanced years. One hundred and eighty-four patients age 45 and under were operated on, and 210 over age 45. One reason why so many people over age 45 were operated on was the fear that the gastric lesion might be carcinoma. This brings up the question of how useful resection of the vagus nerves would be as a substitute for resection in treating these older patients. Certainly the abdominal approach would be necessary but, even with this, the surgeon, as we have come to know well, often cannot distinguish between benign and malignant ulcers at the time of operation. Even quick frozen section in this field is unreliable. In each instance of gastric or pyloric ulcer which the surgeon thinks benign, he must choose between exposing his patient to the higher operative risk which accompanies resection or the higher risk of leaving in malignant disease which accompanies vagus nerve resection. It is our opinion that progress can be made in cutting down the postoperative death rate after resection but that little progress can be made in recognizing

## SUBTOTAL GASTRECTOMY FOR ULCER

early carcinoma in the gross, and we therefore favor a policy of resection for these cases unless clearly contraindicated. This point is well exemplified by an increasing number of cases (some 33 or more) of superficial spreading carcinoma of the stomach observed by us and described by Dr. A. P. Stout of the Surgical Pathology Laboratory, in which the mucous membrane and submucosa are involved alone, and also by the not inconsiderable number of cases with carcinoma in a limited area of an otherwise microscopically benign ulcer.

TABLE VII.—*Partial Gastrectomy for Ulcer. Cases Done Prior to 1936*

### I. Operations in Decade 1926-1935:

A. Followed 10 to 20 Years (Average 13 Years)	—	32 Cases
Present Follow-Up Status:		
Still currently followed.....	25	
Dead, not of ulcer.....	4	
Lost .....	3	
Follow-Up Result:		
Satisfactory .....	26	
Unsatisfactory .....	6	
B. Followed Less Than 10 Years (Average 5 Years)	—	17 Cases
Present Follow-Up Status:		
Dead, not of ulcer.....	6	
Dead, of ulcer .....	1	
Lost .....	10	
Follow-Up Result:		
Satisfactory .....	13	
Unsatisfactory .....	3	
No record .....	1	
C. Postoperative Deaths (12%)	—	6 Cases
TOTAL OPERATIONS 1926 - 1935	—	<u>55</u>

### II. Operations in Decade 1916 - 1925:

A. Followed 10 to 27 Years (Average 20 Years)	—	25 Cases
Present Follow-Up Status:		
Still currently followed.....	14	
Dead, not of ulcer.....	8	
Lost .....	3	
Follow-Up Result:		
Satisfactory .....	21	
Unsatisfactory .....	4	
B. Followed Less Than 10 Years (Average 3.5 Years)	—	19 Cases
Present Follow-Up Status:		
Dead, not of ulcer.....	5	
Dead, cause unknown .....	1	
Lost .....	13	
Follow-Up Result:		
Satisfactory .....	10	
Unsatisfactory .....	4	
No record .....	5	
C. Postoperative Deaths (20%)	—	9 Cases
TOTAL OPERATIONS 1916 - 1925	—	<u>53</u>

The causes of postoperative deaths were often multiple, but the apparent chief causes can be grouped as in Table VI. We are reasonably sure of the accuracy of this table as autopsies were obtained in nine of the 18 fatalities. Among those not autopsied the causes of death were in most instances clear, viz., two pulmonary emboli, one cerebral vascular accident, one coronary occlusion, one aspiration pneumonia, one meningitis. The other three cases not subjected to autopsy had leakage of the duodenal stump which was obviously the main cause of death.



It is to be noted that in this series there was no death resulting from hemorrhage during the immediate postoperative period or from leakage at the suture line at the anastomosis or from obstruction about the stoma. The chief objectives of our efforts to lower the postoperative death rate in the future will be: first, more intensive study of patients over age 50 and their indications and contraindications for radical surgery; second, attempts to lower the incidence of leakage of the duodenal stump (and, in this regard, we believe that the simple Hofmeister post-colic procedure will eliminate, to a considerable degree, the back pressure occurring at times with the anterior types of anastomoses); third, attempts to lower the incidence of pulmonary complications.

The postoperative death rate was 4.6% (18 died in the hospital). To these must be added seven others who died after leaving the hospital as a result of failure of the operation. These cases are included among the unsatisfactory ones listed in Table III. They are as follows: one with proved jejunal ulcer; four with late infection or obstruction; one with severe bleeding from the pancreaticoduodenal vessels; one with pulmonary tuberculosis re-activated by the operation. The patient who died with gastric carcinoma is not included in this list. These bring the operation death rate to 6.4%, if all the patients are included who died of their ulcer or the effects of operation, in the hospital or after they had gone home.

#### PATIENTS FOLLOWED OVER TEN YEARS

In Table VII are given summaries of the resections done for ulcer prior to 1936. Because of the relatively high mortality in those years, the operation was usually done only as a last resort in treatment. In the decade 1916 to 1925, wide resection of the stomach was not done for ulcer. These operations were little more than pylorectomies. During the following decade, 1926 to 1935, more extensive resections were beginning to be done, but rarely as wide as has been standard during the past 10 years. For this reason it is not possible to compare the follow-up results of the three decades with each other. The chief interest in these old cases lies in the number of them who have been followed for 10 years or more.

In the decade 1926 to 1935 there were 55 cases, of whom 40 remained satisfactory, which is 73% of the 55 cases and 83% of the followed cases, omitting the postoperative deaths and one case that was not followed. Of these 40, 27 were followed for 10 to 20 years. None of the cases that remained satisfactory for five years thereafter became unsatisfactory.

In the decade 1916 to 1925, when pylorectomies were being done, there were 53 cases, of whom 31 remained satisfactory, which is 59% of the 53 cases and 80% of all the followed cases. Of the 31, 21 were followed for 10 to 27 years.

In the two decades 1916 to 1935, 15 cases have been followed for 20 or more years and 48 for 10 years or more. Among the cases of the earliest decade are three who became unsatisfactory for the first time after more than five satisfactory years. They are the only ones in our records that did this. They all had what we should now consider inadequate resection and do not

vitate the rule that in carefully followed cases, primary recurrences are rarely found after five good postoperative years where there has been adequate resection.

COMMENT

The above record of the experience of a general surgical service with subtotal gastrectomy for peptic ulcer may help to resolve some of the controversy concerning the form of therapy which should be adopted for these lesions. Certain aspects of this record seem to us to be especially important. These are: 1) The high percentage of excellent results which have followed this operation. Very few of the cases called satisfactory are restricted in their diets, most of them smoke, and many indulge in alcohol. Their life and occupation are not interrupted by recurrence of ulcer symptoms. They are the antithesis of "gastric cripples." Few among them have digestive complaints beyond the range of normal man. There is reason to believe that recurrences among this group in the future will be infrequent because none among them who has gone five years without recurrence later developed symptoms.

2) For people under age 45, resection is a relatively safe procedure, the hospital postoperative mortality in our hands being about 1%.

In view of 1) and 2) and the absence as yet of any studies based on long follow-ups in cases in which vagus resection has been performed, we lack the evidence to justify us in advising our younger ulcer patients to have vagus section performed. We are waiting with keen interest to see the reports of five and ten year results of this experimental procedure. For patients under 45 or 50 years of age, we see little reason for withholding resection. Some patients in this age group, of course, will provide exceptions to those general statements.

3) For patients of the older age group the problem of therapy becomes more complicated. We do not attribute any particular importance to age 45 but about that time the fear of carcinoma comes more frequently into the picture and postoperative troubles multiply. Among this group, patients who have lesions of the stomach which, after careful study, are not free of suspicion of being carcinoma, should as a rule be subjected to resection. In individual cases this rule can be modified depending upon how strong the evidence for carcinoma is and the patient's apparent ability to stand the operation.

It is most difficult to dictate the form of therapy that should be used in people of the older age group whose ulcer is in the duodenum and in whom carcinoma is almost surely absent. If these people bleed, their risk of death is relatively higher than in the younger age group. If their symptoms are intractable under a medical regimen, as they often are, one must consider either a different form of medical therapy or surgery. If surgery is decided upon, the low mortality of vagus nerve section is appealing, provided it is found that it arrests symptoms for long periods, which as yet there has been insufficient time to show.

4) Whereas psychic factors undoubtedly play an important role in relation to ulcers, they have not interfered seriously in many cases in this series with the benefits of surgery. Some of the unsatisfactory cases seem to have an

organic basis for their complaints. On the other hand, not a few patients who gave the impression of being psychoneurotic before operation lost this characteristic after being free of their pain or bleeding. If a patient under 45 has a demonstrable, intractable ulcer, it may be well to relieve him of his organic cause of distress, even if doing so does not wholly free him from functional defects. In these cases especially, is the wise physician most needed.

5) The decade covered by this report includes the war years when the staff of attending surgeons, resident surgeons, anesthetists and nurses were not as complete as it now is. The current postoperative mortality and morbidity during 1946 and 1947 have shown improvement over those of previous years here reported.

6) It is interesting to note the steady improvement in postoperative mortality in a teaching institution during the past thirty years. In the decade 1916-1925 the rate was 20%; in the decade 1926-1935 the rate was 12%; in the decade 1936-1945 the rate was 4.6%; in the two years 1946, 1947, the rate was 2.5%.

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# THE PROBLEM OF PEPTIC ULCER FOLLOWING PANCREATECTOMY\*

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MANN AND WILLIAM IN 1923 demonstrated, in dogs, that after an operation short-circuiting the alkaline duodenal contents, bile and pancreatic juice into the lower small bowel, a marginal jejunal ulcer forms at the gastrojejunostomy site, due to the action of unneutralized gastric juice. This operation consisted of transecting the duodenum at its proximal and distal ends, leaving the bile and pancreatic ducts attached in normal position to the duodenum. The proximal end of the duodenum was closed and the distal end was anastomosed to the side of the lower ileum. The open end of the jejunum was then sutured to the pylorus. (Fig. 1). Fourteen dogs out of a group of 16 thus treated and followed over a period of time developed typical peptic ulcers in the jejunum adjacent to the site of the anastomosis with the stomach. Repetition of this experiment by others has consistently confirmed the results.

In another series of experiments the bile and pancreatic ducts were transplanted to the lower ileum. The majority of animals so treated developed ulcers in the duodenum. Peptic ulcers likewise form in the intestine distal to the pylorus in dogs in which the bile and pancreatic ducts are transplanted into the ileum and in addition the duodenum is resected. On the other hand those dogs in which the duodenum was resected and the bile and pancreatic ducts were implanted into the jejunum at about the same distance from the pylorus as they were originally, remained in good condition for long periods.

Exalto<sup>2</sup> in 1911 and Matthews and Dragstedt<sup>3</sup> in 1932 in similar experiments demonstrated the importance of neutralizing duodenal content in the prevention of peptic ulcer.

Peptic ulcers may form in like manner in man following pancreatoduodenectomy in which the bile duct is anastomosed to the jejunum distal to the gastroenterostomy, and the pancreatic duct, in case of subtotal pancreatectomy, is ligated. One of these procedures was done in each of the following cases.

A man of 59 years was operated upon for suspected carcinoma of the pancreas. At operation the pancreas was hard except for two large cystic areas. It was impossible to determine whether this was carcinoma or pancreatitis or both; therefore, because of the severity of symptoms, total resection of the pancreas was carried out. Pathologic study revealed a severe chronic pancreatitis with an intraductile papilloma obstructing the main pancreatic duct near the ampulla of Vater. The patient made a very satisfactory postoperative recovery except for the development of a postoperative hernia in one portion of the wound.

In restoring the bowel continuity, a proximal anterior gastrojejunostomy and a distal cholecystenterostomy were made. An enteroenterostomy was made

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between the two previous anastomoses (Fig. 2). The patient was well until four months after operation when he was prostrated by sudden severe abdominal pain which came on without warning while he was at work hanging a new window in his home. When seen 24 hours after the onset of symptoms the patient was moribund. Exploration revealed a two centimeter sized perforation of the anterior wall of the jejunum at the site of the gastrojejunostomy. The perforation was closed but the patient died of peritonitis in spite of intensive supportive therapy. Autopsy revealed the surgically closed ulcer and another superficial ulcer adjacent to it at the line of junction of the jejunum and stomach. The entero-anastomosis designed to protect the biliary system from gastric and intestinal content had diverted the bile from the gastroenterostomy stoma leaving the jejunal mucosa to the direct action of unneutralized gastric juice.

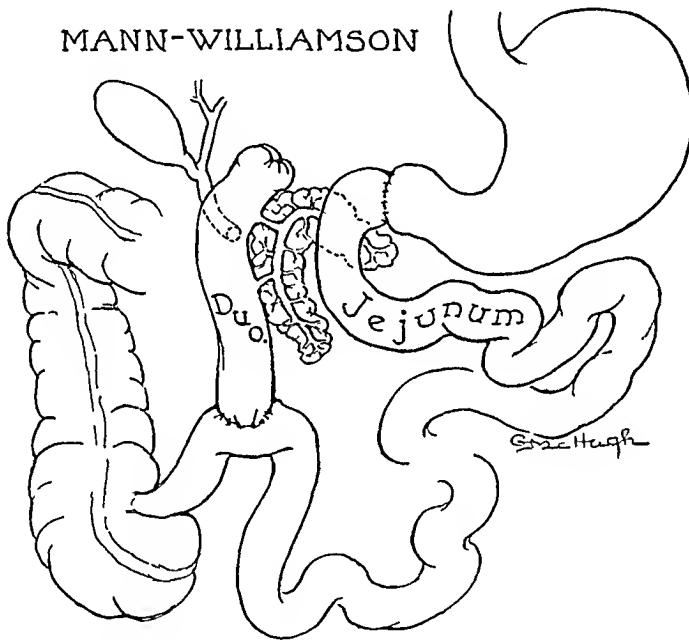


FIG. 1.—Mann-Williamson procedure carried out in first group of animals.

A second man died of carcinomatosis six weeks after resection of the head and neck of the pancreas and at autopsy a benign ulcer with a sinus was found on the lesser curvature of the stomach. The reconstruction in this case consisted of a proximal posterior gastrojejunostomy, distal choledochojejunostomy and intermediate jejuno-jejunostomy. The transected stump of pancreas was ligated. There was failure of neutralization of gastric juice because of diversion of the bile and the absence of pancreatic juice.

The third patient had a resection of the head and neck of the pancreas for carcinoma of the head of the pancreas. A proximal gastroenterostomy, a distal cholecystenterostomy and choledochoenterostomy and an intermediate enteroenterostomy were performed. Closure of the pancreatic ducts was effected by

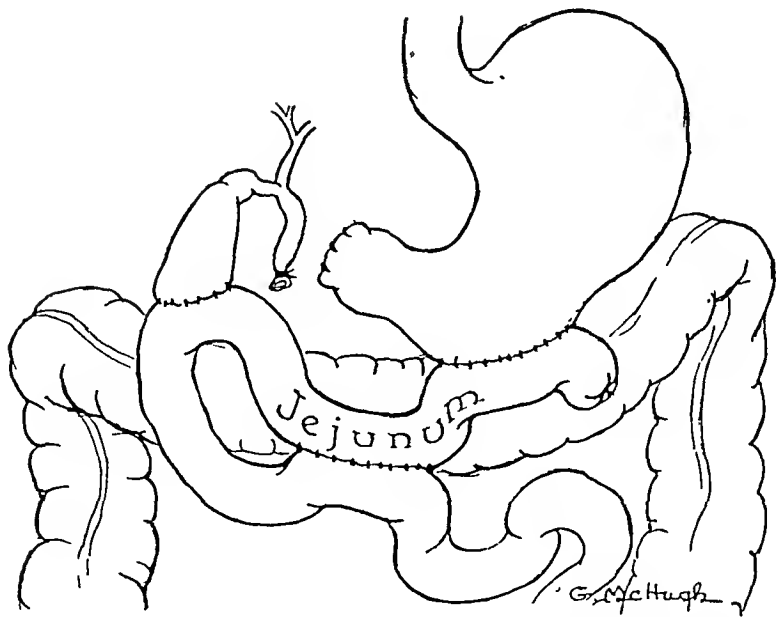


FIG. 2.—Reconstruction of gastro-intestinal tract following total pancreateoduodenectomy in Case No. 1.

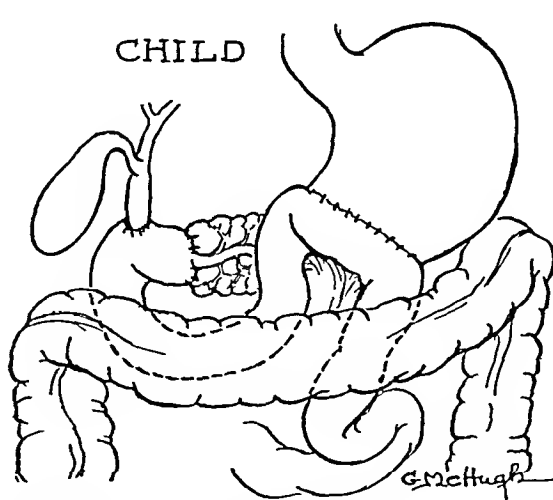
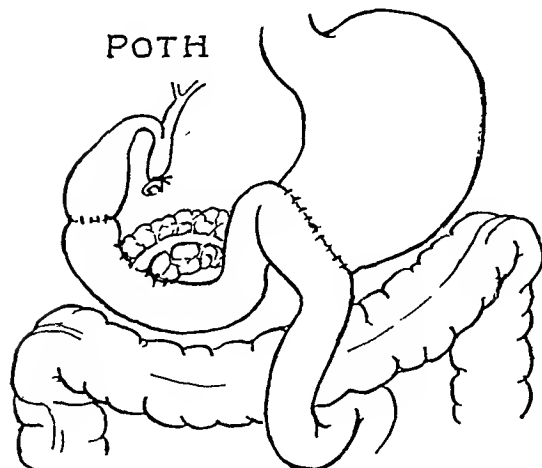
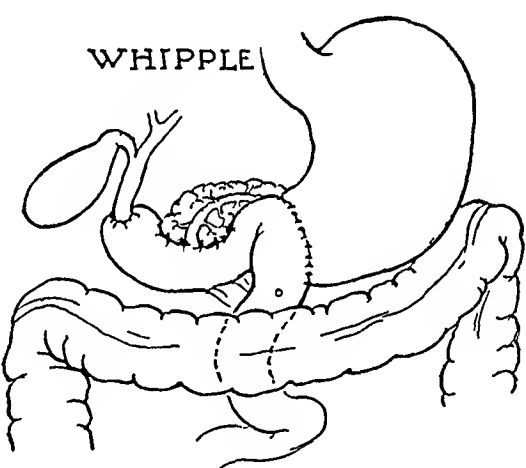
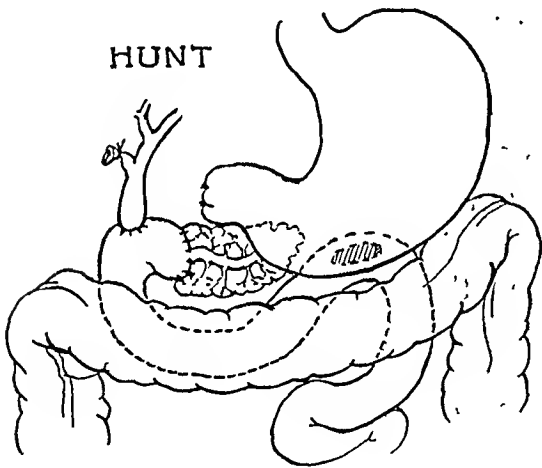


FIG. 3.—Methods of reconstruction which are founded on sound physiologic principles.

ligation and suture of the transected end of the pancreas. The patient made a satisfactory recovery from operation but returned a month later complaining of recurrent epigastric pain coming on about two or three hours after meals. Roentgen-ray examination of the upper gastro-intestinal tract failed to reveal any evidence of ulcer in the gastroenterostomy stoma, but there was a persistent collection of barium present along the lesser curvature of the stomach which was suspicious, but not a typical ulcer pattern. However, this patient responded well to a modified ulcer diet with the addition of magnesium and calcium carbonate powders. He has remained asymptomatic on a modified ulcer diet. The type of reconstruction in this instance resembled that employed in the other cases.

The methods of reconstructing the intestinal tract following the resection of the duodenum and pancreas are so numerous and varied that no attempt will be made to enumerate them. Many of these repairs tend to deprive the patient of the maximum neutralizing effect of the bile, pancreatic juice and duodenal secretions. So much attention has been paid to protecting the biliary passages against the reflux of intestinal content that the problem of protecting the gastroenterostomy has been largely overlooked. The importance of implanting the pancreatic duct into the jejunum in case of partial pancreatectomy can be appreciated when one considers the strong alkaline reaction of pancreatic juice.

The plan of repair published by Hunt<sup>4</sup> in 1941 has the advantage of affording the maximum protection to the gastroenterostomy stoma and at the same time reducing to a minimum the reflux of gastric and intestinal content into the bile ducts. Hunt (Fig. 3) anastomosed the pancreatic duct with the proximal end of the jejunum and implanted the common duct into the jejunum just distal to the pancreatodochojejunostomy. (Fig. 3). Somewhat farther distal was performed the gastroenterostomy. In this patient all of the bile and pancreatic juice passed the gastrojejunostomy site and maximum utilization of the neutralizing effect of these juices was obtained where it was most needed. Whipple<sup>5</sup> in 1943 and Child<sup>6</sup> and Poth<sup>7</sup> in 1944 have used methods similar to that described by Hunt. Child and Poth each removed the antrum of the stomach and made a Polya type of anastomosis. This avoided the blind pouch of stomach left by Hunt and Whipple and slightly reduced the acid secreting area of the stomach. The long jejunal loop made by Poth and Child affords protection to the biliary tree from reflux of gastric content. Waugh and Priestly have recently demonstrated a similar repair. Other methods of reconstruction fail to take full advantage of the protective action of bile and pancreatic juice.

Depriving the body of duodenal secretions by the resection of the duodenum reduces the neutralizing power of the alkaline secretions of the gastro-intestinal tract. Undoubtedly this is a factor of less importance in cases of carcinoma of the pancreas than in benign lesions of the pancreas, for the gastric acidity tends to be reduced in those patients with carcinoma. However,

reconstruction after total or subtotal pancreatoduodenectomy in man should be done in such a manner as to neutralize the gastric juice as fully as possible. The ideal reconstruction operation consists of a choledochojejunostomy and, when a portion of the pancreas remains, a pancreatodochojejunostomy, both performed proximal to the gastrojejunostomy.

Pearse<sup>8</sup> has recently suggested standardizing the reconstruction following pancreatoduodenectomy. He considers the principles of repair to be:

1. The use of retrocolic end to side gastrojejunostomy.
2. The implantation of the common bile duct into the intestine.
3. The reconnection of the pancreas with the intestine.
4. The diversion of the gastro-intestinal contents away from the liver and pancreas by antiperistalsis.

We are in accord with his principles, but emphasize the fact that all bile and pancreatic juice should pass the gastrojejunostomy stoma.

The use of vagotomy in this operation to prevent the formation of ulcer has been considered. There are several objections. First, we feel that the basic repair, if properly done, should not require the added procedure of vagotomy. Second, experimental work done by Dragstedt and co-workers<sup>9</sup> with Mann-Williamson type of dogs reveals that vagotomy protects these dogs only slightly against the formation of ulcers. (46% of dogs with vagotomy developed ulcers, whereas 63% of dogs without vagotomy developed ulcers). Thus we feel that vagotomy is not indicated as an adjunct to pancreatoduodenectomy which in itself is a formidable operation.

#### SUMMARY

1. The importance of the neutralizing effect of bile and pancreatic juice in the prevention of peptic ulcer is emphasized.

2. The development of peptic ulcers following improper reconstruction of the gastro-intestinal tract after pancreatoduodenectomy is cited. Three cases are reported.

3. Recommendations are made for methods of repair after pancreatoduodenectomy which make the greatest use of bile and pancreatic juice in the neutralization of acid gastric juice.

4. Vagotomy is not a substitute for the proper type of reconstructive procedure.

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# EXPERIMENTAL REPAIR OF COMMON DUCT DEFECTS UTILIZING A FREE VEIN GRAFT OVER BLAKEMORE-LORD TUBES \*

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THE REPAIR OF COMMON DUCT DEFECTS and the treatment of stenosis of the common bile duct is an imposing surgical problem. Witness to this is the multitude of operative procedures which are employed today. Treatment of common duct stenosis is difficult in itself, becoming increasingly so when a defect of the duct must be bridged. Proportionally, the longer the defect which is present, the greater the difficulty in repair.

Eliot<sup>1</sup> in 1936 reviewed the various basic methods of repair of cicatricial strictures of the bile ducts which were in use from 1900 on. Many of the methods he discussed are still widely in use today. Two recent developments have contributed a substantial share of success in the treatment of these lesions. Pearse<sup>2, 3</sup> developed a vitallium tube for insertion in duct strictures to maintain patency. This method has been quite commonly used since his original publication in 1942. Cole et al<sup>4</sup> favor the modified hepaticojejunostomy with employment of the Roux loop and baffling of the intestinal wall, especially when a defect is present in the common duct. Pearse<sup>3, 5 6</sup> in a report of 106 collected cases in which the vitallium tubes were used, makes note of the fact that each case in which the tube was used to bridge a gap in the duct resulted in failure. There were seven patients in the series in which this occurred. Pearse also states that the most desirable result is obtained only when an end-to-end anastomosis of the duct stumps can be carried out over a vitallium tube and the tube is left in situ indefinitely. Bettman,<sup>7</sup> Neibling and Walters,<sup>11</sup> and Cattell<sup>12</sup> have shown that biliary obstruction occasionally recurred with the use of the vitallium tube when it became plugged with deposit (bile encrustation), similar to that which occurred in rubber tubes which have been used for the same purpose.

Horsley, in discussing papers by Eliot<sup>1</sup> and Allen,<sup>8</sup> states that one of the earliest attempts in this country to reconstruct the common bile duct was performed by Sullivan in 1900 when he inserted a rubber tube into the hepatic duct and carried it into the duodenum. The indwelling tube was then surrounded with fat and neighboring tissue. Horsley, in 1918, inverted a segment of vein and sutured it into a defect which was made by resecting a portion of the common duct in dogs. He pointed out that the operation was successful from a technical standpoint, but after a few months the vein, being unaccustomed to irritation by bile, contracted and became completely obstructed.

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Dean Lewis, cited by Eliot,<sup>1</sup> related that experimental substitution of the wall of a vein, or other fascial structure, for the excised segment of duct invariably terminated in failure, and furthermore, that all plastic operations in which portions of adjacent hollow viscera were utilized for a similar purpose were unsuccessful and had been discontinued.

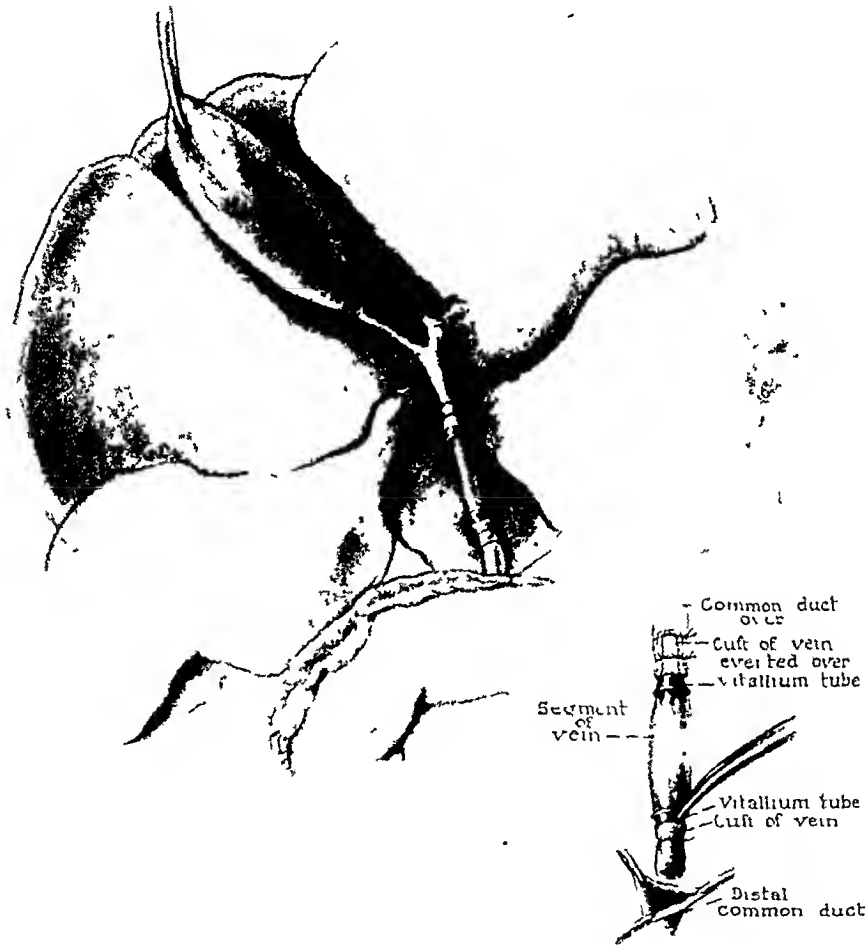


FIG. 1.—Experimental repair of defect of common duct in dogs, utilizing free vein graft and Vitallium tubes. Insert shows technic of implantation of vein graft in common duct

Despite such adverse reports, however, Lord and Chenoweth<sup>9</sup> reported moderate success with the use of fascial and venous grafts over rigid vitallium tubes in the repair of common duct defects. In their experiments the fascial grafts proved most successful. They observed that the venous grafts developed a lining of biliary epithelium over the intima. Marked shrinkage in the length of their grafts occurred, however, and when the animals were sacrificed it was observed that none of the grafts was more than 3 mm. in length.

In the present experiments we are concerned with the repair of an artificially produced defect of the common duct in the dog. It would be ideal to use a pliable, non-irritant material or tissue which would be available in any length, and which would not be susceptible to necrosis or bile encrustation, and, preferably, one which necessitated the use of no suture material. It has been frequently shown that the presence of any of these factors is a definite detriment to the successful repair of a stenotic common duct or one in which a defect is present.

A non-suture method for anastomosis of blood vessels was described by Crile<sup>13</sup> in 1909. Hitchings, working in Crile's laboratory, devised a brass

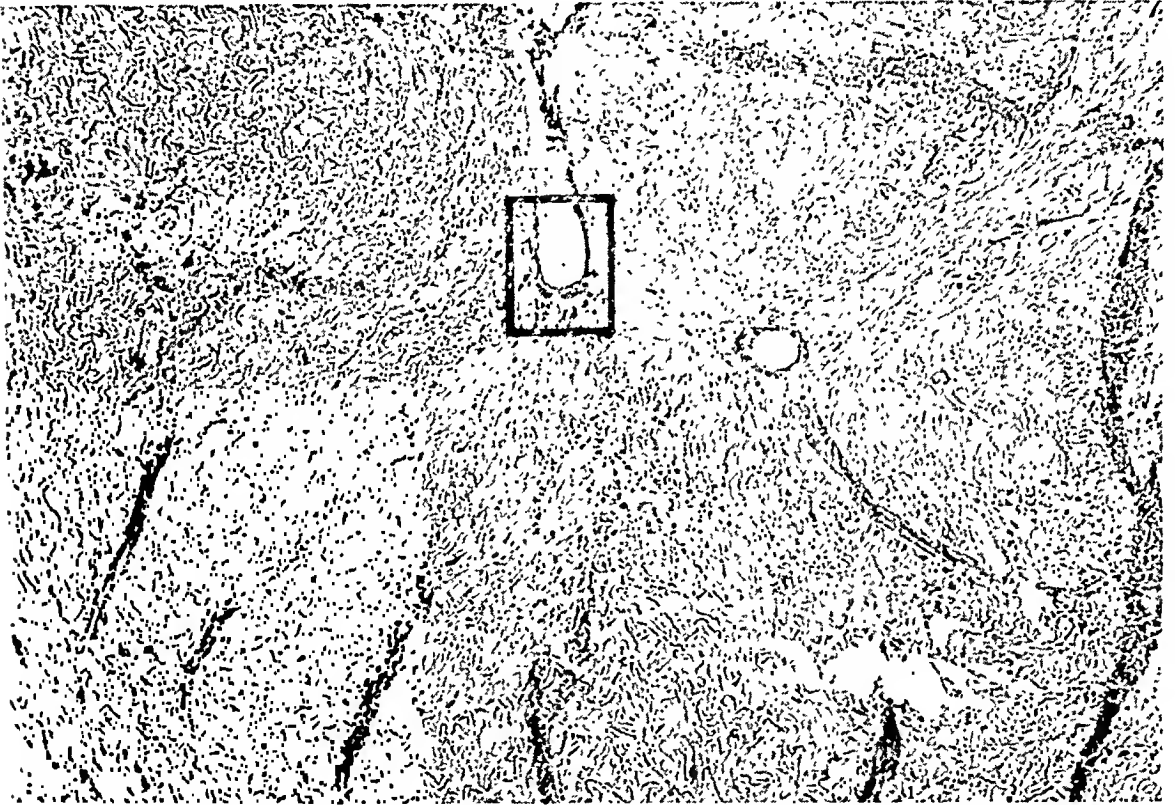


FIG. 2.—Photomicrograph (H & E stain). Free vein graft 88 days after implantation in common duct. There has been partial autolysis of biliary tract epithelium, but low columnar cells are evident in the outlined portion. Van Gieson stain shows the presence of normal elastic fibers. Trichrome stain reveals a normal amount of connective tissue. Cellular infiltration is absent.

cannula over which a vein was cuffed for insertion into an artery for direct transfusion of blood. Shortly after Blakemore and Lord<sup>10</sup> described in detail a non-suture technic for bridging arterial defects, employing special vitallium tubes of their own design, along with a free vein segment, it occurred to us that a defect in the common duct could be similarly bridged.

In contemplation of the problem we were well aware that difficulties such as Horsley encountered might occur. It was noted, however, that in employing this type of graft, no injury to duct epithelium or vein intima from the use of suture material would result, and therefore there would be less predilection to stenosis. Rather than invert the vein, we felt that the endothelium of the

intima would withstand the irritation of bile far better than the adventitia, whose fibroblasts react more quickly to irritation. At the onset, it was also appreciated that several events might occur: first and most important, immediate necrosis and rupture of the vein graft might occur as a result of inadequate blood supply and irritation by bile; second, obstruction might result from edema of the vein wall or encrustation with bile salts; and third, fibrosis and ultimate stenosis might occur from irritation over a long period.

In its favor, however, the employment of the free vein graft over Blakemore-Lord tubes theoretically gave us an agent for bridging a gap in the common



FIG. 3.—Photomicrograph (H & E stain). Bridging channel after free vein graft implantation of 114 days duration. H & E and PTAH stains show biliary tract epithelium lining the lumen. Van Gieson stain reveals the presence of elastic fibers and trichrome stain shows normal connective tissue. Cellular infiltration is absent.

duct which would obviate the use of suture material in the epithelial lining and which presented a medium of adequate length. Also, for all intents and purposes, it is a non-rigid system and one in which a common duct defect can be bridged and still retain the physiologic usefulness of the sphincter of Oddi. This is exceedingly important since ascending cholangitis is such a frequent complication of other types of repair.

We postulated also that there would be epithelialization of the intima of the vein segment with biliary tract epithelium, as reported by Lord and Chenoweth.<sup>9</sup> It was supposed that blood supply to the graft could only be

supplied by vascularization of connective tissue where the graft was interposed in the common duct and the ligature applied, and also from peritonization of the graft and surrounding area.

#### METHOD

Mongrel dogs weighing 14 to 16 kg. were anesthetized with intravenous Nembutal, 1 cc. per 5 pounds of body weight. An intratracheal tube was introduced and intermittent positive pressure controlled respiration was

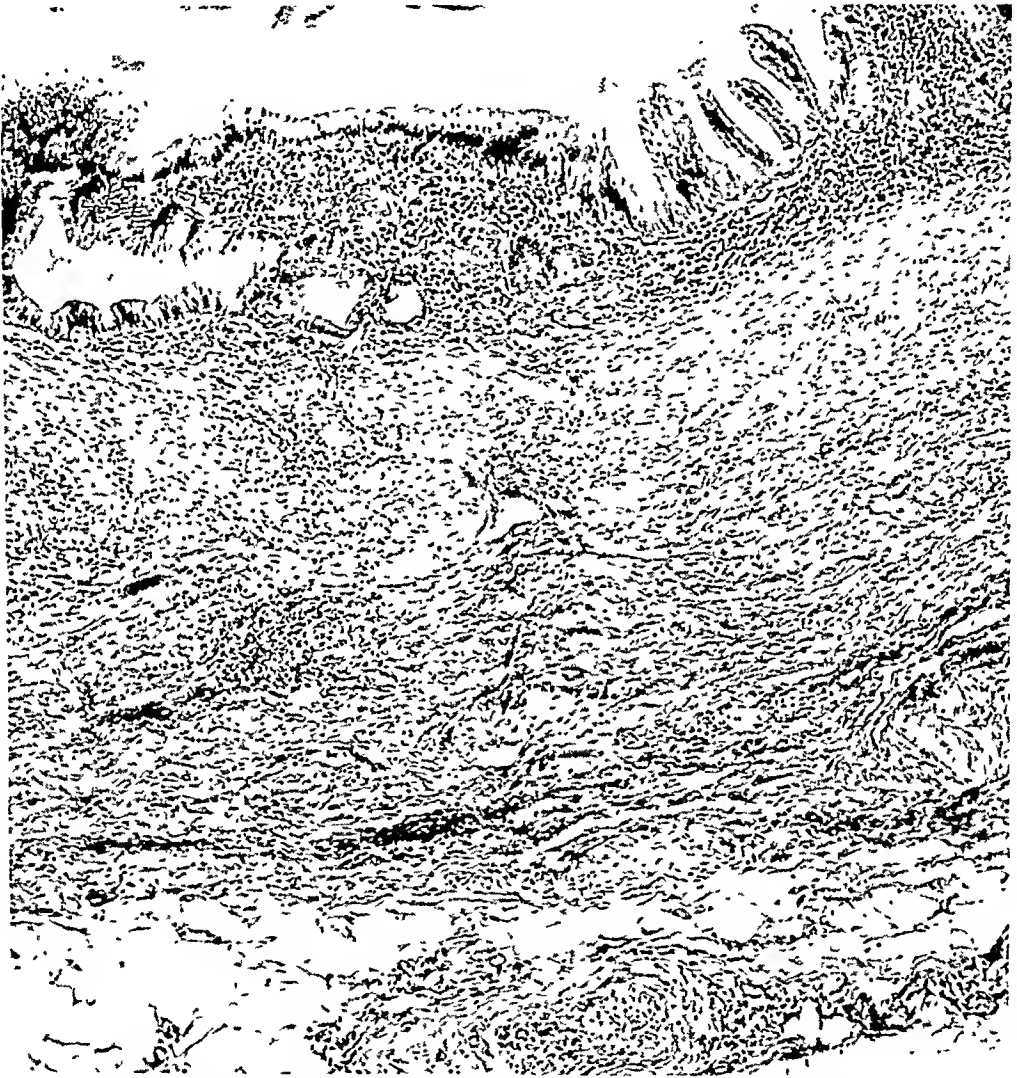


FIG. 4.—Photomicrograph (H & E stain). Bridging channel after free vein graft implantation of 208 days duration. This section, histologically, approaches the appearance of normal common duct seen in Figure 5.

maintained. Using aseptic precautions, a longitudinal incision was made in the left thigh from the knee to the inguinal fold over the femoral vein. The vein was dissected free from the surrounding tissue. All venous tributaries were ligated close to the wall of the vein with 4-0 Deknatel. In each experiment, a segment of vein 5 cm. in length or longer, depending upon the size of the animal, was utilized. Each end was ligated with 3-0 Deknatel and the vein segment excised. The vein segment was then cuffed over 3 mm. vitallium tubes after the method described by Blakemore and Lord<sup>10</sup> in the repair of

arterial injuries. The vein was secured to the tubes with 4-0 Deknatel and the prepared segment was irrigated with physiologic saline to determine its patency and placed in physiologic saline at room temperature. The thigh incision was closed in layers and continuous No. 38 stainless steel wire was used to approximate the skin edges.

A curved transverse incision was utilized to expose the right 9th rib, which was resected along with its cartilage. The thorax was entered through the rib bed and the diaphragm opened in the direction of its fibers. The intestines and stomach were packed away with moist tapes. The common bile duct was identified and mobilized for a distance of three to four cm. in its most distal portion. Two 3-0 Deknatel ligatures were then passed beneath the common

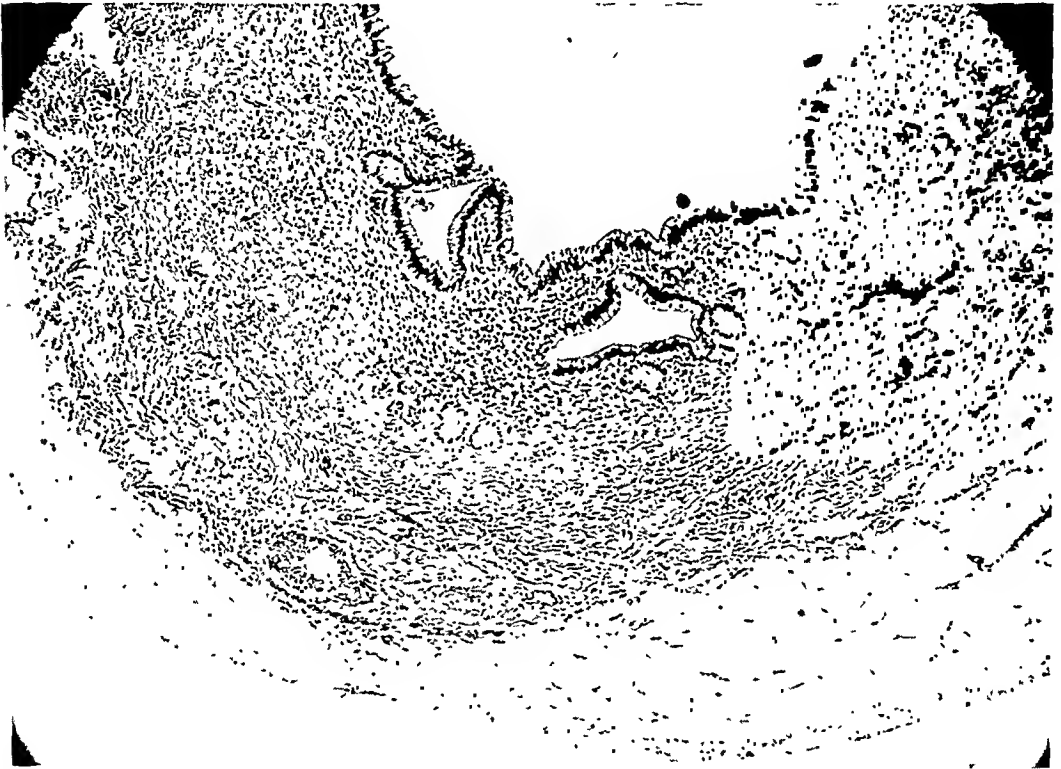


FIG. 5.—Photomicrograph (H & E stain). Histologic appearance of normal common duct of dog.

duct and the duct was then transected about 1.5 cm. for the duodenum, and with retraction of the duct ends, a defect 2 to 2.5 cm. in length was produced. The retracted ends of the duct were grasped with mosquito hemostats and triangulated. A curved hemostat was used to hold the free flange of the Blakemore-Lord tube, and the graft was introduced into the proximal end of the duct and secured with the previously placed ligature. An additional ligature was then placed proximally for security. A similar procedure was carried out in inserting and securing the graft in the distal portion of the duct (Fig. 1). In all instances a free flow of bile was observed at the distal end of the graft

before inserting it into the distal portion of the common duct. No attempt was made to bring omentum over the graft or to peritonize the operative site. The diaphragm was repaired with interrupted 3-0 Deknatel sutures and 100,000 units of penicillin were instilled into the pleural cavity after the partially collapsed lung was re-expanded. The skin was closed with continuous No. 38 stainless steel wire suture which was left in situ throughout the experimental period.

This particular operative approach was found to result in the most satisfactory exposure of the extrahepatic biliary system in the dog. The common duct of dogs of this weight is 3 mm. or less in diameter. In our total series there were no operative deaths.

It must be noted that in our earliest procedures we observed that a short segment of vein retracted in such a fashion as to cause over-riding of the

TABLE I.—*Experimental Data*

No. of Dogs	Experimental Period (Days)	Patent Grafts	Ruptured Grafts	Visible Graft with Obstruction
9	5-26	6	2	1 (a)
5	34-57	3 (b)	0	2 (c)
2 (d)	68-88	1	0	1
4	104-114	4	0	0
1	208	1	0	0
<hr/>		<hr/>	<hr/>	<hr/>
Total 21		15	2	4

(a) In one animal there was partial obstruction, although bile could be expressed through the system from the gallbladder with gentle pressure.

(b) One animal sacrificed at 56 days. another at 57 days. Vein graft was unidentifiable but patent channel was present and bile flowed freely into the duodenum.

(c) One animal was normal until 36 days after operation when jaundice appeared. At autopsy, seven days later, the vein graft was obstructed due to swelling at the proximal tube, but had remained elastic and viable.

(d) Both vein grafts were intact, viable and elastic. One animal became jaundiced and at autopsy dilatation of the common duct proximal to the graft was observed, due to swelling of the graft within the proximal tube.

flanges of the vitallium tubes and a resulting mechanical biliary obstruction. To obviate this, tubes with smaller flanges were used with success. With larger defects to bridge, and with the utilization of longer vein segments, this complication was absent.

## RESULTS

Twenty-one dogs comprise this series and in each a vein graft over Blakemore-Lord vitallium tubes was used to repair a defect of the common duct. Autopsy was performed on all the animals at death or when sacrificed at the end of the experimental period. In each case the extrahepatic duct with the graft in situ was tested for patency by gently perfusing the common duct proximal to the graft with physiologic saline and observing whether the perfusion fluid flowed readily from the ampulla of Vater. At autopsy it was noted that in all dogs that had survived an experimental period of 10 days or more, the previously denuded site of operation and the graft itself were completely covered by peritoneum.



The results are grouped in Table I, according to the experimental period in which the graft was in situ.

In the total series, there were four animals which we considered failures. Early in the series two animals developed absolute biliary obstruction due to swelling of the vein graft within the proximal vitallium tube which in these instances was of 2 mm. size. One dog died as a result of necrosis and rupture of the graft when one vitallium tube became kinked upon the other. The fourth animal developed necrosis and rupture of the graft, along with acute suppurative peritonitis, concomitant with distemper.

We can only consider the result as equivocal in three of the animals. In two instances death occurred as a result of severe distemper on the 16th and 22nd postoperative days, respectively, and it was felt that this experimental period was inadequate. We did observe, however, that these two animals had patent and viable vein grafts, although one showed slight dilatation of the proximal biliary tract. Bile expressed from the gall bladder, however, flowed freely from the ampulla of Vater. A third animal survived 88 days; on the

TABLE II.— <i>Experimental Results</i>				
No. of Dogs	Excellent	Equivocal	Failures	Per Cent
21	14	3	4	66.7
				14.3
				19.0

68th postoperative day this animal developed severe distemper followed by profound jaundice. At autopsy there was severe swelling and obstruction of the graft at the proximal vitallium tube.

Fourteen animals lived 10 to 208 days before being sacrificed. In each, at autopsy, there was a patent channel between hepatic ducts and duodenum.

Nine of these 14 animals still utilized the original free vein graft (Fig. 2). The remaining five animals developed a patent, pliable channel lined with biliary epithelium. The vein segment, in the meantime, had lost its identity and contiguity in the fibrous growth. (Figs. 3, 4.)

#### SUMMARY

A series of 21 animals is presented (Table II) in which a common duct defect was repaired with a free vein graft over Blakemore-Lord tubes. In 14, or 66.7 per cent, of these animals, the resulting bridging channels remained functionally patent and a free flow of bile was maintained. Three, 14.3 per cent, developed severe distemper and the experimental period was considered inadequate, although the vein graft remained viable and elastic. Four, 19 per cent, were described as failures and a discussion of each is presented.

The authors wish to express their appreciation to Carl H. Lenhart, M.D., Professor of Surgery for his help in making this study possible; and to H. Z. Lund, M.D., Assistant Professor of Pathology, who aided in the preparation of photomicrographs and who reviewed the microscopic sections.

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# CONSERVATIVE THERAPY OF RESIDUAL CALCULI FOLLOWING OPERATIONS ON THE COMMON BILE DUCT\*

Report of Two Cases

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RESIDUAL CALCULI are occasionally observed in the common bile duct following operations upon it. Formerly, surgical exploration was required for the removal of these stones. Within the past ten years, however, reports have appeared in the literature concerning the fragmentation and dissolution of these stones by chemical means through the "T" tube indwelling in the common duct. Pribram<sup>1</sup> has reported 38 cases of common duct stone which were cured by the installation of ether and liquid paraffin. He states that a secondary operation was not required in this type of case for at least seven years. He considers that a secondary operation be indicated only if thorough and long therapy with the ether-paraffin has failed. His cases required a maximum of six weeks treatment prior to disappearance of the stones. Walters<sup>2</sup> and Burgess<sup>3</sup> report excellent results in similar patients in whom the Pribram method of treatment was supplemented with the use of nitrites, in order to relax the papillary sphincter. Other investigators have reported success with various solvents such as chloroform<sup>4</sup> and solution "G",<sup>5</sup> and in some cases<sup>6</sup> nupercaine has been used successfully.

It is imperative to relieve the obstruction produced by calculi in the biliary tract. When a "T" tube remains in the common duct, however, it is uncommon to have evidence of liver damage or other sequelae of common bile duct obstruction. Conservative management of such cases would be particularly indicated. In the cases reported below, a trial of conservative therapy for three months in one patient, and for eleven months in the other, resulted in complete disappearance of the stones. Freedom from symptoms followed removal of the "T" tube in each case.

## CASE REPORTS

**Case 1.** S. D., white male, age 38, was admitted to the medical service of Dr. H. Goldburgh, at the Jewish Hospital, Philadelphia, on October 22, 1945. His chief complaint was abdominal pain and colic of five days duration, which had been followed, after 24 hours, by increasing jaundice, anorexia, and nausea. No vomiting was experienced. Stools were acholic. There was a previous attack of pain and jaundice in 1944, one year preceding this present episode. On admission, the patient presented moderate pallor and severe jaundice. There was marked muscle guarding in the right upper quadrant of the abdomen. No mass was palpable and no tenderness was present.

Laboratory studies revealed a hemoglobin of 16.5 gm., red blood cell count of 5.1 million per cu. mm., white blood cell count of 8.2 thousand per cu. mm., with a normal differential picture. Urine had a pH of 5.0, specific gravity of 1.013 to 1.024, bile and

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urobilinogen were present. Bile pigment was identified in the feces. Blood sugar was 88 mg. per cent; blood urea nitrogen was 15 mg. per cent; and the blood cholesterol was 286 mg. per cent with 70 per cent esterification. Prothrombin time was 125 per cent of normal. Serum amylase was 86 units. Icterus index was 38 units on admission, and it fluctuated from 28 to 42 units during the preoperative course.

After adequate preparation, the patient was transferred to the surgical service of Dr. F. B. Block. Operation was performed November 3, 1945. The abdomen was opened through a right rectus incision. The gallbladder contained stones. The common bile duct was filled with a creamy, inspissated material, but a calculus was not demonstrated in the common duct. The gallbladder was removed and a "T" tube placed into the common bile duct.

Postoperative convalescence was uneventful. On the eleventh postoperative day a cholangiogram indicated that dye was not passing into the duodenum. At that time, the duct was lavaged through the "T" tube with 3-4 cc. of ether. This was repeated daily,

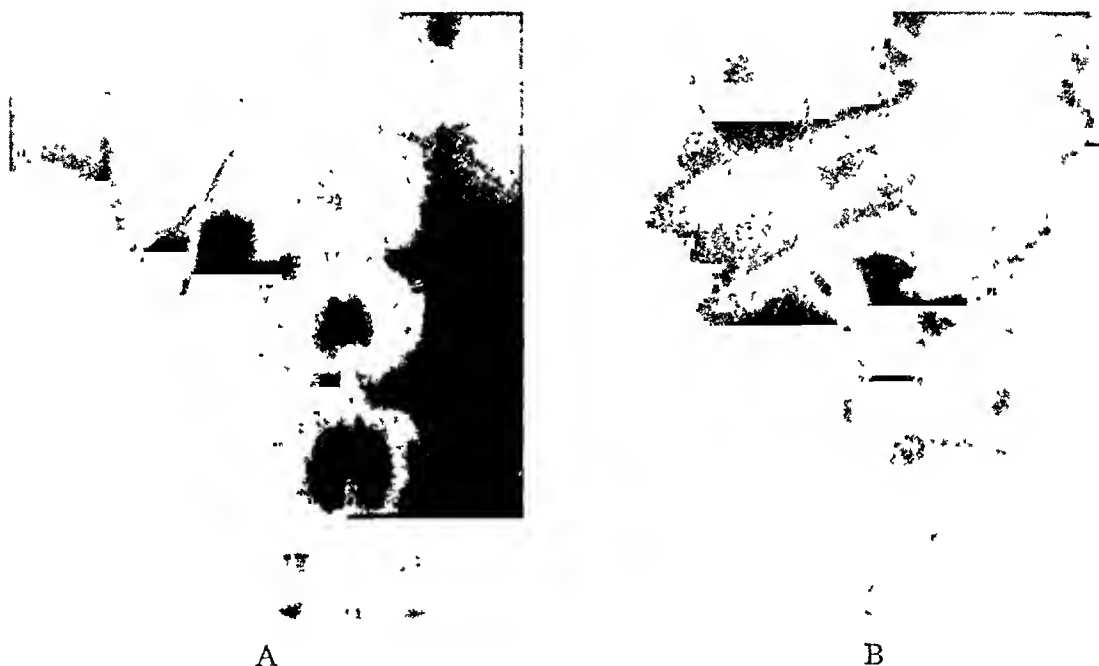


FIG. 1A.—*Patient S.D. Before Ether Therapy.* Notice tremendous dilatation of common bile duct and radiolucent defect at distal end of duct. No flow of diodrast into the duodenum is seen.

FIG. 1B.—*Patient S.D. After Ether Therapy.* Duct now normal size. Radiolucent defects gone. Free flow of contrast medium into the duodenum is evident.

usually without discomfort to the patient. If pain appeared, inhalation of amyl nitrite was sufficient to control it. Repeated cholangiograms were done on November 20 and 27, 1945. These indicated a calculous obstruction at the distal end of the common bile duct, associated with retrograde dilatation of the common and hepatic ducts. (Figure 1a) Dye did not pass into the duodenum during the roentgen study. On several occasions, solution "G," instead of ether, was used to perfuse the duct, but the patient did not tolerate this material.

During this period, the patient's icterus index returned to normal values. Repeated tests of liver function were returned at normal levels. The patient was discharged from the hospital on November 27, 1945, with the "T" tube left in place. He had been instructed in the management of the irrigations of the common bile duct using the ether injection. This was continued daily while the patient was at home.

Two months later, on January 9, 1946, a cholangiogram revealed that there was free flow of the contrast medium into the duodenum. The biliary ducts were minimally dilated, and there was no longer any evidence of calculous obstruction at the distal portion of the common bile duct. (Fig. 1b) In view of the fact that this patient had been asymptomatic for five weeks, the "T" tube was removed.

This patient has remained well. Follow-up examinations have shown absence of jaundice or pain, and complete freedom from any complaints referable to the biliary or gastro-intestinal tract, for 18 months since the removal of the "T" tube.

**Case 2.** F. K., white female, age 54, was admitted to the Surgical service of Dr. F. B. Block, at the Jewish Hospital, on October 1, 1946. Her chief complaint was severe colicky abdominal pain, accompanied by indigestion of 36 hours duration. The pain, which originated in the right upper quadrant, radiated under both costal margins.

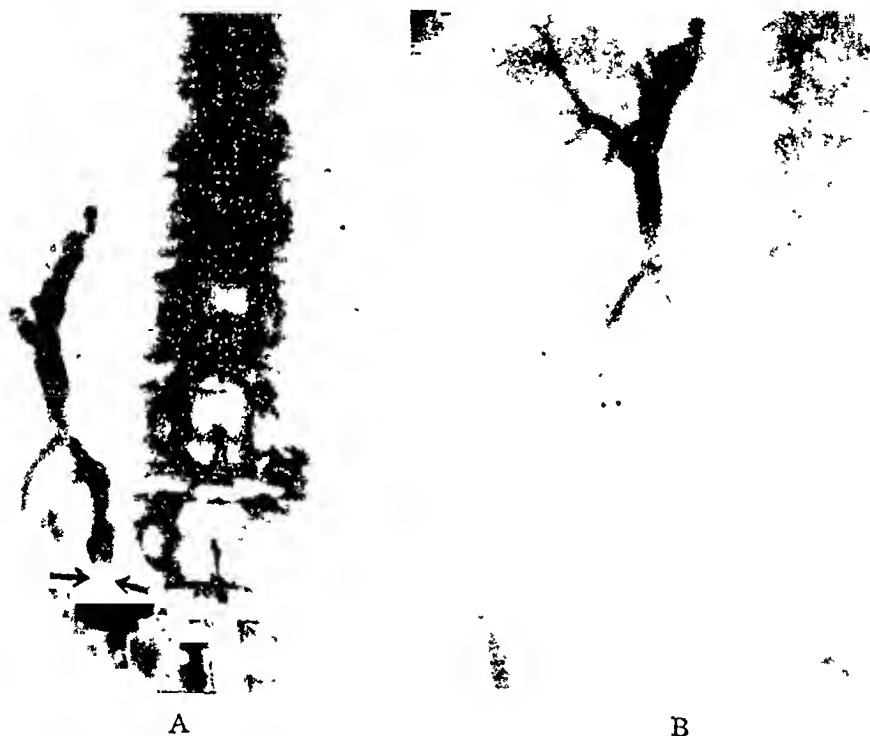


FIG. 2A.—Patient F.K. Before Ether Therapy. Common duct somewhat dilated. Radiolucent defects indicating stones at distal end of common bile duct (between arrows). Obstruction is not complete, as evidenced by the presence of the contrast medium in the small intestine.

FIG. 2B.—Patient F.K. After Ether Therapy. Radiolucent defects not present. Common duct not dilated. Diodrast present in duodenum.

There was no nausea or vomiting. Stools were normal in character and appearance. On examination this middle aged woman looked acutely ill. Her abdomen was moderately obese. Marked tenderness and rigidity were found in the right upper quadrant. A tender mass in the right subcostal region, difficult to outline, was interpreted as enlarged gall-bladder. No jaundice was noted. Peristalsis was normal. A cystocele and rectocele were discovered as incidental findings.

Laboratory studies indicated the hemoglobin to be 13.7 Gm., and the white blood cell count was 20,600 per cu. mm., with 91 per cent polymorphonuclear cells. Urine had a pH of 6.0, specific gravity of 1.010; there was no sugar, albumen, or bile present. Urobilinogen was present in the urine in 1:20 dilution. Blood icteric index was 20 units,

TABLE I.—*Intra-choledochal pressure readings (Case Two)*

Date	Initial Pressure (cm H <sub>2</sub> O)	During increasing amounts of solution			Pain Threshold (cm of H <sub>2</sub> O)	Vol. in duct (cc.)	Remarks
		5 cc.	10 cc. (all in cm of water)	20 cc.			
5/11	6	15	30	—	32	11	150 cc. of solution; sluggish flow; tiny mucoid particles in return flow.
5/12	4			30	30	15	450 cc. of solution; severe pain followed; pigment debris present.
5/15	0		17	25	25	5	500 cc. of solution at 30 cm. of water press. Residual fluid clear; free flow.
5/16	0	8		26	26	11	250 cc. of solution at 40 cm. of water pressure residual fluid clear; free flow.
5/17	0	10		20	32	14	200 cc. of solution at 50 cm. of water pressure. Residual fluid clear; free flow.
5/19	0				28	0	300 cc. of solution at 60 cm. of water pressure. Residual fluid clear; free flow.

and the blood serum amylase was 455 units. Blood sugar, urea nitrogen and serologic examinations were normal.

A diagnosis of acute pancreatitis associated with cholelithiasis was made presumptively. This patient was treated conservatively. She was given oral and parenteral feedings of proteins and carbohydrates reinforced with adequate vitaminotherapy. Her clinical status improved rapidly. After one week, the icterus index was 6 units, and the blood amylase had decreased to 83 units. With subsidence of the acute episode, a cholecystogram was done. This revealed marked decrease in gallbladder function. Bromosulfalein test for liver function revealed that no dye was retained in the blood stream at the end of 45 minutes.

Operation was performed on October 12, 1946. The abdomen was opened through a right rectus incision. Exploration was limited to the gallbladder, common bile duct, and immediately adjacent tissues. There was marked edema of the area about the cystic duct and the ampulla of the gallbladder. Adequate dissection of this region was prohibited by the extent of the inflammatory process. The common duct was opened, and approximately eight small faceted stones were removed. Irrigation of the duct returned clear fluid, and there was no interference of flow of the irrigating fluid into the duodenum. A "T" tube was sewn into the common bile duct. A partial cholecystectomy was done. The gallbladder bed was drained.

Examination of the gallbladder revealed beginning gangrene of the mucosa, with evidence of chronic cholecystitis. Multiple faceted calculi were present in that organ. On section, these calculi were composed of an outer brittle layer of white material and a soft pigmented nucleus. The outer shell was fragmented rapidly, and partially dissolved within ten minutes of the stone's immersion in ether.

The patient's postoperative course was normal. She was ambulant on and after her first postoperative day. Oral intake was sufficient and the patient generally comfortable. Stools were normal in color and no icterus was present. The "T" tube was clamped on the 10th postoperative day, without clinical signs or symptoms.

A cholangiogram was done on October 25, the 13th postoperative day. A radiolucent shadow was noted in the terminal portion of the common bile duct, and several shadows which resembled calculi were noted in the hepatic duct radicles. Three to four cc. of ether were injected daily thereafter through the "T" tube. The injections produced moderate discomfort.

Cholangiogram was repeated on October 29, 1946, at which time diodrast passed from the common duct into the duodenum. A persistent dilatation of the common and hepatic ducts was visualized. Radiolucent defects were present at the distal end of the common duct and in the hepatic duct proximal to the hepatic limb of the "T" tube. (Fig. 2a)

The patient was instructed to irrigate the long limb of the "T" tube once to twice daily with three to four cc. of ether. She was discharged from the hospital on November 1, 1946, but returned on November 9, 1946, because of recurrent colicky pain which accompanied perfusions of the duct. During this admission, physical examination revealed no jaundice, mass, fever, or any physical abnormalities. A cholangiogram showed that the shadows previously reported were less numerous and had moved to a more distal position in the ducts. In addition, the cholangiogram revealed that there was less dilatation of the hepatic ducts.

She was discharged after four days observation with instructions to irrigate the tube as before. It was the clinical impression that the lavage was inducing fragmentation of the calculi, and that her episodes of pain were due to small pieces passing through the papilla of Vater. She was advised to inhale amyl nitrite should any of these episodes become distressing.

These irrigations were continued for three weeks until December, 1946, after which the irrigations were done two to four times weekly. On several occasions she suffered

mild colic or indigestion, but without disability of more than a few hours.

On May 11, 1947, the patient was readmitted to the service of Dr. F. B. Block for repair of the cystocele and rectocele. During this admission a cholangiogram revealed that a radiolucent shadow resembling a stone was present in the papillary area of the common bile duct.

The duct volume and intraductal pressures were measured on several occasions. (Table I.) The volume of fluid contained in the common bile duct varied from eight to 15 cc. This indicated that the duct was now of normal size. Pressure readings were generally normal, since pain appeared at 30 cm. of water, and the duct emptied at 20 to 32 cm. of water.

Pressure studies were also used as therapy. During each succeeding installation of perfusing fluid, pressure levels were increased progressively in an attempt to increase the fragmentation of the residual calculus, and to permit passage of debris through the papilla. Initially, 10 cc. of 1% metycaine solution was used prior to the installation of any perfusing fluid. Subsequently, all procedures were accomplished with 0.1% novocaine in normal saline. A maximum of 500 cc. of solution was perfused at any one time. The basis for this therapy was a recent report<sup>6</sup> and previous successful experiences by one of the authors (JAS).

At all times perfusing fluid entered the duodenum. During earlier tests, there was marked resistance to flow; and moderately severe discomfort was suffered by the patient. Following the procedure on May 12, 1947, and its attendant severe colic of three hours duration, all other procedures were easily tolerated. At no time, thereafter, was any obstruction encountered to the irrigations.

Despite clinical evidence of the free flow of bile, and of the normal volumes in the common bile duct, cholangiogram revealed that the radiolucent shadow persisted in the papillary region of the common bile duct. No evidence of dilatation of the biliary radicles was present.

The patient was discharged from the hospital on May 25, 1947, following full convalescence from the vaginal plastic operation. The "T" tube remained in position and was irrigated several times weekly with ether for the next three weeks. After this period, the "T" tube was clamped shut continuously.

After several months of complete freedom from all symptoms, a cholangiogram was performed on September 10, 1947. At this time, there was uninterrupted flow of diodrast into the duodenum, and no evidence of calculi. (Fig. 2b)

The "T" tube was removed on September 17, 1947, 26 days short of one year since its insertion. The tube was encrusted with bile stained and inspissated putty-like debris. The sinus drained but a few drops of bile stained mucoid material for 24 hours. The wound has been completely dry since then. There have been no signs or symptoms of biliary tract or gastro-intestinal tract disturbance and the patient is completely comfortable more than ten months after the removal of the tube.

#### DISCUSSION

The literature contains several case reports of success in the conservative management of residual choledocholithiasis following operations on the common bile duct. These stones may not have been observed, or may have been inaccessible at the time of the operation.

Such calculi can produce total obstruction to bile flow, although the obstructive phenomena are usually incomplete and intermittent. Some stones may disappear spontaneously through disintegration, or pass into the gastro-intestinal tract through the papilla of Vater or through an artificial fistula. Others may<sup>7</sup> become imbedded in the wall of the papilla, as in a diverticulum of the duct. Some stones can remain as asymptomatic foreign bodies.



The usual indications for surgical removal of such residual calculi in the common bile duct are:

- (1) complete biliary tract obstruction with progressive jaundice.
- (2) recurrent pancreatitis.
- (3) advancing liver damage.
- (4) recurrent suppurative cholangitis.

It is advisable to avoid secondary procedures on the biliary tract since the risk of reoperation is great and because the technical procedure is frequently very difficult.

It is felt that surgical intervention can be delayed in those patients in whom biliary flow is adequate, and in whom liver function is not impaired. It is similarly thought that conservative management is advisable in patients who are symptomatically comfortable, and who do not present evidence of gross infection. Lavage of the common bile duct through an indwelling "T" tube can be expected to produce excellent results in the therapy of residual choledocholithiasis, if given a trial for a sufficient time.

It should be noted that ether boils at body temperature. This phenomenon is the usual cause for patient discomfort, since the expanded vapours can exert considerable pressure. This in itself is an added advantage because of an increasing pressure increment thus introduced. It is recommended that only three to four cc. of ether be instilled in the common duct during the initial perfusions. If discomfort occurs, the syringe may be disengaged and the ether permitted to bubble out of the open end of the "T" tube. Nitrites may be administered for relief of pain, or prior to the injection in order to relax sphincteric action at the termination of the common bile duct.

#### SUMMARY

Two patients who were treated surgically by cholecystectomy and choledochostomy for calculous disease of the biliary tract were found to have calculi remaining in the common duct postoperatively. In one case, daily instillations of ether during a two-month period were followed by the disappearance of the stone. In the second case, instillations of ether were continued for seven months. In addition, lavage of the duct was done on occasions, using novacaine solutions under increasing intraductal pressure. In this case, stones were not present in the common duct eleven months after their initial recognition. Following the removal of their "T" tubes, both patients have remained asymptomatic.

It is recommended that conservatism be used in similar cases whenever possible because of the technical difficulties of reoperation and the greater risk to the patient. It is also recommended that gall stones removed at operation be saved, and tested for solubility in ether and other solvents, in the event that this information is required in the treatment of the complication of residual common duct stones.

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# BLOOD FAT LEVELS FOLLOWING SUPRADIAPHRAGMATIC LIGATION OF THE THORACIC DUCT

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CONSIDERING THE GREAT VARIATIONS in anatomic configuration and relationships of the human thoracic duct,<sup>2, 3, 9</sup> inadvertent severing of this structure during the course of surgical procedures in the supradiaphragmatic region appears to be a relatively uncommon accident, rarely occurring more than once or twice in the experience of any one surgeon. With the ever-growing frequency of extra- and intrapleural operations, however, there is reason to anticipate that the number of such accidents will increase.

The flow of chyle in the thoracic duct may be interrupted in one of two ways, i.e., by section or ligation. Instances in which the duct has been severed have been more frequently reported in the literature than those in which it has been ligated. Its section results in chylothorax, a complication regularly attended by considerable morbidity in the form of asthenia, inanition and progressive emaciation and not infrequently terminating fatally (1, 5, 13, 14). In a review of the literature up to 1937, Shakelford and Fisher reported an over-all mortality of approximately 50 per cent. Surgical ligation of the duct, on the other hand, does not result in chylothorax and for this reason is attended by a much less severe morbidity than severance.

Both accidents afford unusual opportunities for furthering our understanding of the role of chyle in human bodily economy. Unfortunately, advantage of such accidents has not always been seized by clinicians, so that there remain as yet many obscurities in our understanding of the physiology and pathology of chyle that might otherwise have been illuminated. In view of this, it appears desirable that increments to our knowledge, whether great or small and whether or not documented by oft-repeated observations, should be communicated as they become available.

Of the human studies thus far recorded, the majority have been made in connection with chylothorax, attention having been focused mainly upon the chyle recovered from the chest cavity rather than upon the altered biochemistry of the blood and other bodily fluids. The data acquired permit a fair estimate of the quantity of chyle produced under conditions of chylothorax, namely, 130 to 200 cc. per hour. Certain physical and chemical characteristics of the recovered chyle have also been determined—its alkaline reaction, specific gravity between 1.012 to 1.020, total fats between 0.5 to 3.0 Gm. per cent, total proteins between 1.0 to 6.0 Gm. per cent, and an albumin-globulin ratio of 3:1.<sup>5, 9, 14</sup>

\* Submitted for publication, January 1948.

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tive of a mild degree of cardiac muscle damage. A six-foot plate of the chest demonstrated clear lung fields and a Danzer Ratio of 0.49. The intravenous pyelograms were considered normal.

A diagnosis of essential hypertension was made and the patient was considered a suitable candidate for surgery.

*Operation, December 4, 1946:* General anesthesia was induced under endotracheal nitrous oxide inhalation and maintained by the intravenous administration of pentothal sodium. A 7 cm. segment of the right tenth rib was resected. Its head was distarticulated and the corresponding transverse process removed by the rongeur. A plane of cleavage between the parietal pleura and chest wall was developed. The pleura was then retracted so as to give access to the sympathetic chain from the eighth dorsal to the first lumbar paravertebral ganglia. These ganglia and the intervening segments of the chain were

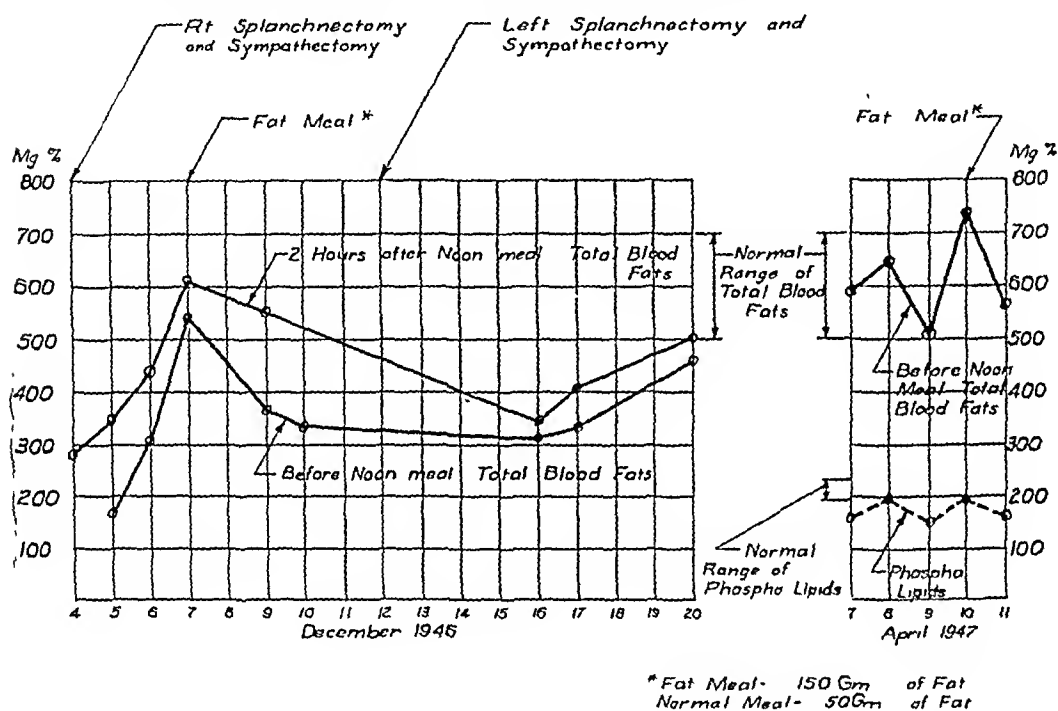


FIG. 1.—Graph showing postoperative levels of blood fat and phospholipids.

ligated and removed. During the ensuing exploration a structure regarded as the greater splanchnic nerve was encountered. A one-inch segment was doubly ligated with black silk and transected between ligatures, whereupon a droplet or two of chyle exuded from the cut end, leaving no doubt as to the structure attacked. The distal portion of the ligated duct immediately began to swell and soon attained a diameter slightly greater than that of a common lead pencil. The splanchnic nerves were subsequently identified somewhat closer to the midline than ordinarily encountered. They were doubly ligated and a segment approximately one inch in length was removed from each. A silk "sleeve" was secured over the proximal stumps. The operator had quite evidently mistaken the thoracic duct for the greater splanchnic nerve.

The patient's postoperative course was uneventful. Symptomatically, she offered no complaints other than of "soreness" at the operative site. To all objective clinical examinations she appeared normal.

Within three hours of the ligation of the thoracic duct and before the ingestion of food, the total blood fat level was 280 mg. per cent. On each of the ensuing three days, total blood fat determinations were made immediately preceding and again two hours

following the noon-day meal. These data\* demonstrated a marked reduction of blood fat levels below the normal range of 500-700 mg. per cent (See Fig. 1).

On December 7th, the third day following operation, a high-fat diet of 150 Gm. was given the patient in order to ascertain its effect on the blood fats. The total blood fats—both before and after the noon-day meal—were discovered to be just within the lower limits of normal range.

Further determinations of blood fat levels under ordinary dietary conditions were resumed on the following day and repeated at intervals up to the sixteenth postoperative day. They continued at subnormal levels but there was observable a gradual trend in the direction of normal.

Splanchnicectomy and sympathetic ganglionectomy were carried out on the opposite (left) side on December 12, 1946, this time without untoward incident. The patient made an uneventful recovery and was discharged from the hospital on the ninth postoperative day.

In order to afford a degree of assurance that the data obtained in the case above reported are not generally characteristic of hypertensive patients of the type who qualify for sympathetic surgery in accord with our criteria, three patients (E. R., female, and K. S. and F. J. males) were subjected to preoperative determinations of total blood fats and phospholipids. Postoperative determinations were made at the 24th, 48th, and 72nd hours and thereafter every other day, the last specimens being drawn on the seventh postoperative day. In none of these were the levels of blood fats or phospholipids found to deviate from the accepted ranges of normal. In this group of subjects, the lowest recorded blood fat level was 500 mg., the highest 780 and the mean, 615 mg. per cent. The lowest recorded phospholipid level was 184 mg., the highest 300 mg. and the mean, 225 mg. per cent.

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\* The methods employed for the determination of total fats and phospholipids in the present study are those devised by Gibson, Lowe and Morrissey (unpublished).

For determination of total fat, 5 cc. of plasma or whole blood is mixed with 25-30 cc. of 90% alcohol. The total mixture is swirled slowly within a 125 cc. Erlenmeyer flask. The flask is heated in a steam bath for 10 minutes and is then allowed to cool. Sixty cc. of diethyl ether are then added. The liquid is filtered through a funnel plugged with fat-free cotton into an evaporating dish. The flask is washed out with several portions of ether and the liquid is pressed out of the solid mass in the funnel with a glass rod. The filtrate is evaporated on a steam bath, care being exercised not to heat the dish once drying has been accomplished. The fat is now dissolved out with several 10 cc. portions of petroleum ether, each portion being evaporated to a volume of approximately 5 cc. The liquid is now filtered through a small, fat-free filter paper into a weighed dish and evaporated on the steam bath. The dish is kept in a vacuum dessicator for 20 minutes and is then weighed. Calculations:  $\text{Gain in weight} \times 20 = \text{mg. per cent of total fat}$ . The normal value in plasma by this test is from 500 to 700 mg. per cent.

For determination of phospholipids, the fats are washed into a 125 cc. Erlenmeyer flask with several 2 cc. portions of petroleum ether. The liquid is then swirled slowly while 3 volumes of acetone and 3 drops of saturated magnesium chloride solution in 95% alcohol are added. The solution is placed in the icebox for 15 to 30 minutes, during which time the phospholipids flocculate. The mixture is now filtered into the weighed dish referred to above. The flask is carefully washed with several portions of acetone, the washings being poured through the filter. Evaporation is carried out to dryness in the steam bath. Exercising the same precautions as those recommended above, the dish is cooled for 20 minutes in the vacuum dessicator and again weighed.

Calculations.  $\text{Loss in weight} \times 20 = \text{mg. per cent of phospholipids}$ . Normal values by this method are 180 to 230 mg. per cent.

## DISCUSSION

The earlier animal experiments in this field suggested that physiologic derangements consequent upon ligation of the thoracic duct(s) are incompatible with life. However, Munk and Friedenthal<sup>8</sup> and D'Errico<sup>4</sup> adduced the first evidence contrary to this view and in 1922 Lee<sup>6</sup> conclusively demonstrated its incorrectness.

Lee studied the postprandial distribution of chyle by feeding cats in whom the thoracic duct had been ligated a cream diet stained with Scharlach-R and Berlin Blue. The animals were sacrificed at periods varying between one and 77 days following operation, and anatomic studies were carried out. Two types

TABLE I  
TOTAL BLOOD FATS PHOSPHOLIPIDS

DATE	(Mg. %)	(Mg. %)
Dec. 4, 1946 a.m.	—	
p.m.	280	
Dec. 5, a.m.	164	
p.m.	346	
Dec. 6, a.m.	306	
p.m.	440	
Dec. 7,* a.m.	542	
p.m.	612	
Dec. 9, a.m.	364	
p.m.	552	
Dec. 10, a.m.	336	
p.m.	—	
Dec. 16, a.m.	312	
p.m.	340	
Dec. 17, a.m.	335	
p.m.	404	
Dec. 20, a.m.	455	
p.m.	500	
Apr. 7, 1947 a.m.	586	156
Apr. 8, a.m.	643	193
Apr. 9, a.m.	502	144
Apr. 10,† a.m.	736	190
Apr. 11, a.m.	560	154

\* On High Fat Diet, 150 Gm.

† Fat Meal at Noon.

of newly established collateral channels were demonstrated: (a) those to the right thoracic duct and (b) those to the azygos vein and/or its branches. All this was, of course, consistent with the traditional concept of the transit of fats *from* the gut *to* the bloodstream by way of the thoracic duct.

That the movement of fats may and probably regularly does occur also in a direction opposite to that traditionally visualized, i.e., *from* the blood stream *to* the thoracic duct, was demonstrated in 1944 by Reinhardt, Fishler and Chaikoff.<sup>12</sup> These investigators injected radiophospholipids into the blood stream and were able to recover between 9 and 20 per cent of the lipids from the thoracic duct within three to six hours. It would be a matter of considerable interest to conduct a similar investigation under circumstances in which the thoracic duct is ligated before the injection of phospholipids.

The blood fat levels in our single human experience following ligation of the duct are at variance with the animal findings reported in 1904 by Munk and

Friedenthal.<sup>8</sup> These authors encountered an increase in blood fats, whereas we encountered a decrease. The reasons underlying this disparity of findings can only be speculated upon. A theoretically defensible mechanical account can be made out for either circumstance. It may prove possible to reconcile the disparities in terms of individual and/or species differences in respect of potential collaterals.

In the clinical and experimental studies thus far reported there appears to be a general agreement that following the development of chylothorax and chyloperitoneum the level of blood fats falls off. Shackelford and Fisher<sup>13</sup> summarized their own experiences and those of previous observers in this connection. They considered that the intravenous re-infusion of chyle recovered from the chest cavity has a somewhat salutary effect in raising the blood fat level and in combating asthenia and inanition.

The earliest recorded instance of inadvertent section of the thoracic duct incidental to splanchnicectomy and sympathectomy appears to be that reported upon by Crafoord in 1941.<sup>2</sup> In this case, the duct was severed at the level of the eleventh rib. The distal stump was crushed with a hemostat and buried in the adjacent mediastinal tissue. No untoward clinical manifestations developed. At the time of operation, Crafoord observed one undamaged branch of the duct and he was inclined to ascribe the fortunate outcome of his case to the presence of this vessel. He expressed the belief that when well developed lymphaticovenous anastomoses exist, ligation of the main trunk may be carried out without serious complication. He considered that when such anastomoses are deficient, clinical symptoms must supervene.

In 1942, Whitcomb and Scoville<sup>15</sup> reported a second case of accidental section of the duct in the course of splanchnicectomy and sympathectomy. In this instance, the duct was severed at the level of the first lumbar vertebrae and the distal stump was closed off by the application of a silver clip. For the first week, the patient's postoperative course was uneventful. Thereafter, signs of increasing respiratory embarrassment became evident. Chylothorax was then demonstrated and was dealt with by frequent thoracentesis. The patient's serum protein and fat levels fell off progressively and emaciation became severe in spite of the re-infusion of chyle recovered from the pleural cavity. The patient expired three weeks after operation under circumstances considered by the authors as indicative of anaphylactic shock. Permission for autopsy was not obtained but the authors postulated that the silver clip might have produced necrosis of the duct or that it might have become disengaged.

The available evidence leaves little room to doubt that the organism tolerates ligation of the thoracic duct far more readily than its section. The dynamic factors underlying this circumstance appear to hinge upon the matter of the restitution of homeostasis. Following ligation, a new gradient of hydrodynamic pressure is at once established within a *closed* system. This gradient tends to promote the opening of potential collaterals and the development of supplementary channels. Following section of the duct, the preexisting pressure



gradients are actually increased, falling off rapidly from the "head of pressure" in the villi and mesenteric lymph channels to the cut end of the distal stump. The mechanical factors tending to promote the establishment of alternate pathways for the chyle are, under such circumstances, of negligible character. The result of this is a continuing and poorly compensated biochemical disequilibrium.

It seems unnecessary, therefore, to urge that when the duct is accidentally severed every effort should be made to isolate and carefully ligate the cut ends, particularly the distal stump. For such purpose, a silk suture ligature appears to afford greater security than that offered by mere crushing or clipping. In cases where it is not feasible to isolate the leaking stump, it may prove advantageous to suture a muscle stamp into place or to press a pledget of Gelfoam impregnated with thrombin and plasma against the opening.

The further management of the case should be guided by clinical developments and the results of repeated determinations of blood fat and serum-protein levels. If the latter should fall to levels that appear to threaten physiologic economy, the deficit can be dealt with by increasing the fats and proteins in the diet or by the parenteral administration of plasma, "Amigen" or other commercial preparations of the sort routinely employed in maintaining nutrition in the presence of severe burns and extensive decubitus ulcers.

#### SUMMARY

1. The flow of chyle may be interrupted in the course of extra- or intrathoracic surgical procedures by inadvertent section or ligation of the thoracic duct. The great variations in anatomic pattern of the duct and in its relations to the splanchnic nerves requires that the surgeon be constantly on guard against such accidents.
2. Section of the thoracic duct is productive of chylothorax, a serious and often fatal complication characterized by respiratory embarrassment, asthenia and inanition. Ligation of the duct may be unaccompanied by subjective complaint and in any case is productive of a much less serious physiologic disorder than its section.
3. A case is reported in which, following inadvertent ligation of the thoracic duct, blood fat levels were determined throughout a period of sixteen days until physiologic levels were regained and maintained. The blood fat level was sharply reduced immediately after the accident to half its normal value. During the next two weeks, it gradually climbed to normal levels. A high fat diet (150 Gm.) temporarily restored the blood fats to low-normal levels. Clinically the patient exhibited no ill effects.
4. If the thoracic duct is accidentally severed at operation, every endeavor should be made to close the opening by suture ligature. Where this proves unfeasible, a muscle stamp or "Gelfoam" pledget should be employed. Postoperatively, the blood fat and serum protein levels should be determined at regular intervals. The frequency of such determination will depend upon the degree of biochemical disequilibrium demonstrated. If indicated, special

dietary and/or intravenous measures may be adopted in order to furnish needed fats and serum proteins.

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# STREPTOMYCIN IN SURGICAL INFECTIONS

## PART V. Infections of Soft Tissues

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THIS COMMUNICATION, the fifth of a series dealing with the streptomycin therapy of surgical infections in U. S. Army hospitals, is concerned with the results of this form of antibiotic therapy in infections of the soft tissues. The composite material on which it is based consists of case reports submitted to the Office of the Surgeon General and subjected by us to critical analysis, with the object of determining the present status of this antibiotic in the management of infected wounds. The ultimate goal of this investigative effort is to identify the indications for, the dosage of, and the adjuvant utility of, streptomycin in the treatment of impending and established wound infection.

### REVIEW OF LITERATURE

To date, only a small number of reports have been published concerning the use of streptomycin in soft tissue infections. Two of these were experimental studies. Kirby<sup>1</sup> and his associates produced virulent infections in dogs by traumatizing the spinal muscles and contaminating the wounds with cultures of staphylococci, streptococci, and colon bacilli. Both local and invasive infections were controlled when streptomycin was applied locally at the time contamination was introduced or when it was given parenterally every six hours for six days. All untreated animals, however, developed severe infections and 55 per cent of them died.

Howes<sup>2</sup> experimental study, which antedated that of Kirby and his associates, concerned streptomycin and sulfamylon (sulfabenzamine hydrochloride). He produced infections in the spinal muscles of rabbits by traumatizing them and introducing either cultures of bacteria or dirt scraped from the floor. Local injection immediately after injury of a solution containing 0.2 per cent streptomycin and 5 per cent sulfamylon prevented the development of infection. Infection was not prevented, however, if drug treatment was delayed three hours or more unless secondary wound excision was done concomitantly. Once infection had become established, treatment with the solution described failed to hasten resolution.

The few clinical studies reported in the literature are not conclusive. White<sup>3</sup> observed clinical improvement in respect to the type of granulation present and in respect to decrease, decolorization and thinning of drainage in 18 of 32 amputation stumps after local treatment for 24 to 72 hours prior to wound revision and skin grafting with packs soaked in 0.1 per cent solution of streptomycin. The remaining stumps were not improved, and neither in the improved

\* Submitted for publication, February 1948.

nor the unimproved cases were organisms eliminated consistently. Hirshfeld<sup>4</sup> reported that granulations became healthy and grafts took well in four sloughing or granulating wounds when streptomycin was applied topically in 0.05 per cent solution over an unspecified period of time. The bacterial flora was not altered, however, and the resistance to streptomycin increased remarkably. The results were disappointing when the drug was used parenterally in other types of soft tissue infections. Poor results were attributed to the presence of streptomycin-resistant organisms in mixed infections.

Keefer<sup>5</sup> and his associates, who supplied no details, stated that six patients with surgical wound infections had improved on parenteral or topical streptomycin therapy. Brooke<sup>6</sup> reported that in 10 cases of infected wounds, ulcers and burns, "good results in general" followed the topical application of 0.25 per cent parachlorophenol and 0.5 per cent streptomycin in a carbowax base for six to 30 days. Finally, M. E. Florey<sup>7</sup> reported that five out of six chronic sinus tracts residual to battle incurred injuries with predominantly gram-negative flora, became sterile when treated with streptomycin. All healed within three weeks of the end of treatment. The exceptions contained *Staphylococcus aureus* and *Streptococcus hemolyticus*, which were not eliminated until topical penicillin was applied.

#### MATERIALS AND METHODS

The basis of this report is 102 streptomycin-treated infections of soft tissues in males of military age, including 67 cases of cellulitis, 33 of which were associated with abscess formation, 30 cases of localized infection, and five cases of specialized infection. The series represent all instances of infection observed over a given period of time. No fresh wounds are included. They represent a selection of cases, such as occurs in civilian practice, in which only patients refractory to standard methods of treatment reach the hospital for treatment and study.

Sixty-eight of the 102 patients were treated with streptomycin alone and 34 were treated with a combination of streptomycin and other bacteriostatic agents. The results of therapy were classified on the basis of the type of clinical response as good, doubtful, and poor.

*Bacteriology.*—Gram-positive cocci were the dominant organisms in 61 of the 102 cases which make up this series. *Staphylococcus aureus* and hemolytic streptococci were found in pure culture, alone or in combination in 20 cases, and gram-negative bacilli were cultured alone in 16 cases. Mixed infections were present in 20 cases. In the remaining five cases, there was no drainage.

The cultures of bacteria were tested for streptomycin sensitivity in all but five cases. Eighty-five per cent of the gram-negative bacteria were found to be sensitive, that is, they were inhibited in vitro by concentrations of streptomycin easily maintained in the blood stream (16 micrograms per milliliter or less). Eighty per cent of all staphylococci and streptococci were streptomycin sensitive, and the remaining 20 per cent were only moderately resistant. All anaerobic gram-positive bacilli tested were insensitive.

## ANALYSIS OF RESULTS

## Streptomycin Treated Cases

Streptomycin was the only antibacterial agent employed in the treatment of 68 cases (Table I). The results were classified as good in 47, doubtful in seven, and poor in 14. Details of the first 27 cases follows:

*Improved Group.*—Eight of the 12 patients regarded as benefited by streptomycin therapy had cellulitis, in five instances associated with abscess formation, and four had localized infections.

Two of the three patients with cellulitis without abscess formation were treated by the intramuscular route. The first patient, who had myelogenous leukemia, had a cellulitis in the cervical region from which streptomycin-sensitive *Salmonella typhimurium* was cultured. The second, three days after excision of a pilonidal sinus with primary closure of the wound, developed an infection from which streptomycin-sensitive *Escherichia coli* and hemolytic streptococci were cultured. In both instances prompt resolution of the inflammatory process and satisfactory healing followed treatment with streptomycin.

TABLE I.—*Results of Therapy in 68 Infections of Soft Tissues  
Treated by Streptomycin Only\*\*\**

DIAGNOSIS	No. of Cases	Range of Dose**	RESULTS		
			Good	Doubtful	Poor
Cellulitis .....	18	1.8—3.0	15	1	2
Cellulitis with abscess.....	26	1.0—2.4	25	1	
Wound suppuration* .....	10		7	2	1
Sinus tracts .....	8	1.0—1.5			8
Septic burns .....	3	2.4		2	1
Chancroid .....	1	2.4			1
Meloidosis .....	1	2.4			1
Decubitus ulcer .....	1	2.4		1	
Total .....	68	1.0—3.0	47	7	14

\* In Gm. per day.

\*\* Applied topically, in concentrations of 1-10 mg. per milliliter.

\*\*\* This table was remade after the article was prepared for publication, so as to the author's 41 cases, 13 of cellulitis, 21 of cellulitis with abscess, 6 of wound suppuration, and 1 septic burn. The entire series suggests that streptomycin parenterally administered in doses of 2.0 to 3.0 Gm. a day is equally effective as penicillin against gram positive coecal cellulitis and cellulitis with abscess caused by streptomycin susceptible organisms.

The third patient with non-localizing cellulitis developed the infection 15 days after a plastic operation on the hand which included tendon transplants, and tendon, fascial and bone (iliac) chip grafts. Culture revealed *Proteus vulgaris* and *Staphylococcus aureus*, both sensitive to streptomycin. The wound was re-opened under parenteral streptomycin protection and infected. necrotic tendon and fascial grafts were removed; the bone chips and tendon transplants were maintained. Localization of the infection was observed within 48 hours and supplemental topical application of streptomycin by means of wet dressings was followed by the formation of clean, bright red granulations and good wound healing.

In all five cases of cellulitis with abscess formation localization followed a more rapid pattern than is ordinarily observed following drainage only. Results

were prompt and permanent in four cases: (1) a presacral decubitus ulcer in a paraplegic treated by the parenteral route; (2) a mixed wound infection, due to gram-negative and gram-positive streptomycin-sensitive organisms, treated by the local and parenteral routes; (3) an inguinal infection following an old gunshot wound treated by drainage and parenteral streptomycin; and (4) an infection following repeated aspirations of a seroma complicating cranioplasty. In the latter case which was treated with intramuscular and topical streptomycin, removal of the tantalum plate was necessary.

In the fifth case of cellulitis with abscess formation the course was less smooth probably because the initial streptomycin therapy was inadequate. A recurrent draining infection in the left groin, associated with embedded shell fragments of small size and caused by streptomycin-sensitive gram-positive cocci and *Proteus vulgaris*, was first treated by daily instillations of a 0.5 per cent streptomycin solution followed by streptomycin in an ointment base. Healing was prompt, but two days after it was apparently complete there was a severe recurrence, manifested by local pain, chills and fever. Streptomycin was given parenterally for four days, after which local therapy was substituted. Localization and spontaneous drainage had occurred through the original wound during parenteral treatment and healing again seemed satisfactory. Two weeks later a second recurrence was treated for eight days with 0.4 Gm. of streptomycin every four hours intramuscularly. Resolution of this abscess occurred within 48 hours with spontaneous drainage. This third course of treatment, which was the first adequate course, apparently resulted in sterilization of the wound and there has been no recurrence in the ensuing eight months.

The four cases of localized infection treated successfully by streptomycin illustrate the ability of this drug to eliminate susceptible bacteria persisting in wounds in which no slough is present. One infection, following radial neurotomy, had not responded to drainage, wet dressings, and treatment by other bacteriostatic agents over a period of six weeks. When topical streptomycin therapy was introduced, cultures which had previously yielded streptomycin-sensitive *Pseudomonas aeruginosa* became sterile within six days and drainage ceased on the tenth day of treatment. Healing thereafter was satisfactory.

The other three cases in this group were all low-grade infections in anophthalmic sockets caused by streptomycin-sensitive coagulase-positive hemolytic *Staphylococcus aureus*. These infections, which ordinarily respond well to penicillin, seemed to respond equally well to instillations of aqueous sterile streptomycin solution (5 mg. per milliliter) two or three times daily for three to five days. The chief advantage of streptomycin over penicillin in such cases lies in the fact that it is thermostable, so that solutions can be warmed to body temperature and the patient's comfort thus be increased. This advantage, however, would be outweighed by the possibility of the development of drug-fastness if the organisms were not eliminated promptly.

*Doubtful Cases.*—Streptomycin was of possible value in two cases in

which it was used prophylactically and postoperatively. The first was a decubitus ulcer of the heel, from which *Escherichia coli* was cultured. Primary healing followed surgical excision and pedicle flap closure. In the second case appendectomy for acute disease was necessary in a patient with *Pseudomonas aeruginosa* infected second and third degree burns of the entire abdomen. The postoperative course was without incident and it was thought that the exudate from the burned area was considerably reduced while streptomycin was being given.

*Poor Results.*—Nine of the 13 patients who did not respond satisfactorily to streptomycin therapy had draining sinus tracts of diverse origins. One followed nephrectomy and three followed wounds of the bladder. In one of the latter cases the organisms had become resistant to streptomycin and did not respond to a second course of therapy, although a previous course had resulted in closure of a suprapubic wound. In a similar case the organisms were resistant initially to streptomycin. In still another case, five courses of streptomycin therapy, all adequate, produced no results. The unsatisfactory outcome in all these cases suggests that streptomycin therapy alone is unlikely to be followed by closure of a fistulous tract connected with the bladder if the sinus has become chronic and scar tissue is present. The causative organisms may be sensitive to the drug in vitro, but surgery must be combined with streptomycin if the desired results are to be attained.

Other cases in this group included a sinus following perforation of the splenic flexure with an intraperitoneal abscess, in which the organisms were found to be streptomycin-resistant before therapy was undertaken; a sinus of the buttock following retroperitoneal trauma; a complicated fistula-in-ano for which fistulectomy was performed; a sinus following coccygectomy; and multiple sinuses of the scrotum and peri-anal region in a patient with chancroid. The last two cases deserve special comment. In the infection which followed coccygectomy the exudate became scanty and gram-negative organisms were eliminated, but gram-positive varieties persisted and became drug-fast. Chemotherapy was ill chosen in this case. Obliteration of the tract could not have been anticipated without surgical collapse of the bony wall. The patient with chancroid had a progressive, two-year history of multiple draining sinuses in the scrotum, perineum and inguinal and pubic areas, from which *Hemophilus ducreyi* sensitive to streptomycin was repeatedly isolated. Several courses of parenteral streptomycin therapy, two of which were supplemented by penicillin and sulfathiazole, produced only transient improvement. Recurrence was prompt after the cessation of treatment. The organisms eventually became drug-fast.

There were four chronic localizing infections. Infection remained in two open amputation stumps because removal of necrotic tissue was not complete. Decrease in the discharge during therapy was deceptive in that it was not permanent. The third patient had a chronic cervical abscess caused by *Malleomyces mallei*. In vitro streptomycin resistance of the organisms was

established, but treatment over 57 days, as a last resort, was ineffective. The fourth patient had extensive badly infected third degree burns of both legs and one arm. There was a progressive decrease in the amount of exudate during treatment, but some of the organisms became refractory to the drug. While skin grafting was finally successful, surgical elimination of sloughing tissue, and not streptomycin therapy, was regarded as the dominant factor in reducing the severity of the infection.

#### COMBINATION-TREATED CASES

Results in the 34 cases treated by streptomycin in combination with penicillin or sulfadiazine or both (Table II) were good in 14, doubtful in four, and poor in 16.

*Good Results.*—In this group of cases in which treatment was successful there were 13 instances of cellulitis, one with abscess. There were four caused by *Staphylococcus aureus*, four were caused by gram-negative bacteria, and

TABLE II.—*Results of Therapy in 34 Infections of Soft Tissues  
Treated by Streptomycin and Other Bacteriostatics*

DIAGNOSIS	No. of Cases	Range of Dosage*	R E S U L T S		
			Good	Doubtful	Poor
Cellulitis .....	16	1.5—3.0	12		4
Cellulitis with abscess.....	4	1.8—3.0	1		3
Wound suppuration**.....	2		1	1	
Sinus tracts .....	7	2.4		3	4
Ischiorectal abscess .....	3	3.0			3
Bacterial synergistic gangrene .....	1	2.4			1
Actinomycosis .....	1	1.8—2.4			1
Total .....	34	1.5—3.0	14	4	16

\* Streptomycin in Gm. per day. Sulfadiazine was given in doses of 6 Gm. per day and the minimum dose of penicillin was 240,000 units per day.

\*\* Applied topically, in an ointment base containing 5 mg. of streptomycin per Gm..

three were found to have mixed gram-positive and gram-negative organisms. No cultures were obtained in two cases. Penicillin in adequate doses (ranging between 240,000 and 1,000,000 units per day) had not been successful in controlling the infection in any of these cases, but the prompt, and sometimes dramatic, results achieved following the addition of streptomycin to the therapeutic regimen seemed to point to it as the responsible agent. Streptomycin therapy was considered responsible for the favorable outcome in the case of cellulitis with abscess caused by staphylococci resistant to penicillin but sensitive to streptomycin. The infection, following a cartilage transplant to the nose, showed no improvement after 18 days of penicillin therapy.

A case of localized staphylococcic infection was found in a traumatic ulceration of the lower abdominal wall. In spite of topical and parenteral penicillin therapy the infection had reached the anterior rectus sheath by the forty-first day, and presented a crater on the surface measuring 5 by 10 cm. The local application of 0.5 per cent streptomycin in a water-in-oil emulsion base resulted in complete healing by the 31st day of treatment; all organisms had disappeared from the wound by the twenty-seventh day.

*Doubtful Results.*—In four cases the prophylactic administration of strep-



tomycin may have been helpful in securing uncomplicated primary wound healing. A decubitus ulcer of the leg, in which *Escherichia coli* was the predominating organism, was treated by excision and pedicle flap closure. A sinus tract in the leg, not originating in bone, from which penicillin-resistant, streptomycin-sensitive *Staphylococcus aureus* was isolated, could be treated by split thickness skin graft four days after irrigations with 1 per cent streptomycin solution were begun. A sinus tract following cholecystectomy, which had drained for eight months, was successfully closed, the only complication being a seroma in the wound which yielded no growth on culture. Culture in this case yielded *Staphylococcus aureus* and *Bacillus proteus* resistant to penicillin but sensitive to streptomycin.

The fourth case in this group was a sinus following nephrectomy performed two years earlier but shown by pyelography and lipiodol injections not to be connected with the urinary tract. Penicillin-resistant *Staphylococcus aureus* was cultured from the purulent exudate released at operation. Penicillin and streptomycin in sterile dried plasma powder (1:5) was applied locally at each dressing and successful plastic closure of the wound was accomplished within a short time.

*Poor Results.*—The 16 cases in which combined bacteriostatic treatment was not successful included a variety of conditions. Three ischiorectal abscesses and four cecal fistulas did not respond to various combinations of local and parenteral streptomycin. In one case of furunculosis the original infection was apparently controlled at the end of seven days, but other furuncles appeared 14 days later while the patient was still under treatment. In a second case of furunculosis, severe dizziness and nausea made it necessary to discontinue the drug at the end of 24 hours. Two patients, submitted to tenorrhaphy for battle-incurred injuries of the hand, developed severe postoperative infections which did not improve until wound revision was performed. In another case, massive cellulitis of the groin, with extravasation of urine as a late complication of traumatic rupture of the urethra, was treated by incision and drainage after 1 Gm. of streptomycin had been given daily for two days. Transient improvement was followed by the formation of additional abscesses; treatment in this case was carried out for only five days and was plainly inadequate. In one case of cellulitis following removal of the lower half of the fibula for osteomyelitis, and in another of infection following cartilage graft of the nose, no treatment was satisfactory until the wounds were revised. In the former case, considerable necrotic tissue was present and in the latter, the implant had to be removed. In one case of abdominal actinomycosis which had developed a year and a half after drainage of an abdominal abscess, there had been no response to numerous other forms of therapy, including penicillin, and improvement was only transient after each of three adequate courses of parenteral streptomycin therapy.

The last case in this group of failures was of particular interest. Typical postoperative synergistic bacterial gangrene developed after incision and

drainage of a peritoneal abscess, and by the fifth day the gangrenous area was approximately 15 cm. in diameter. The infection advanced rapidly, in spite of debridement (which was only partial because of the risk of evisceration), penicillin and sulfonamide therapy, until it involved the rectus muscle and extended into the fascial planes. Streptomycin was given intramuscularly, in combination with other therapy, in doses of 4 Gm. daily for five days. It was no more effective than other treatment had been and the patient eventually succumbed to the progressive infection.

#### REACTIONS

Exclusive of pain at the site of injection, of which numerous patients complained, undesirable reactions were recorded in eight of the 61 cases treated by streptomycin. No reaction occurred in patients receiving less than 2 Gm. of the drug daily. In four instances, the undesirable effects were noted after only brief periods of therapy. In two patients, severe dizziness and nausea developed on the first and second day of treatment, respectively. In one of these cases, the drug was withdrawn but in the other, treatment was continued without difficulty with streptomycin from another batch. In two other cases, a generalized rash appeared on the eighth and twelfth days of treatment, respectively. In both instances the drug was withdrawn. The rashes disappeared promptly. In the four remaining cases, vertigo followed the administration, respectively, of 50 Gm. of streptomycin over a period of 16 days, 54 Gm. over 30 days, 104 Gm. over 35 days, and 114 Gm. over 57 days. In every instance withdrawal of the drug was followed by prompt subsidence of the disturbance.

An analysis of these cases shows, as has previously been demonstrated, that streptomycin is a relatively safe drug when it is administered in doses up to 3 Gm. daily for as long as 14 days. Longer courses of therapy may be associated with labyrinthine disturbances, the severity of which is usually in proportion to the duration of therapy.

As these reactions indicate, streptomycin is an agent which has toxic potentialities. No serious permanent sequelae were noted in any case in this series, but it is obvious that the effective dosage of 3 Gm. daily is close to the critically toxic level. Any means of reducing the effective daily dosage would therefore be desirable.

#### COMMENT

Although 61 streptomycin-treated infections of the soft tissues do not constitute a large series; the cases are sufficiently representative to indicate both the possibilities and the limitations of streptomycin as an adjuvant in the therapy of wound infections in soft tissues. At the present time, therefore, it seems possible to make certain definite statements concerning this bacteriostatic agent.

Good results cannot be expected from streptomycin therapy unless certain conditions are met:

(1) The organism (organisms) responsible for the infection must be streptomycin-sensitive.

(2) The drug must be given in adequate dosages.

(3) There must be little or no necrotic tissue present.

(4) The blood supply to the affected site must be adequate.

The cases in this series in which poor results followed streptomycin therapy were almost without exception cases in which the principles laid down for its use were violated. Many of them illustrated the unfortunate but rather general tendency to institute chemotherapy or antibiotic therapy without regard to the fundamental principles of surgical management. In four cases the organisms were known to be streptomycin-resistant. In two cases the dosage was inadequate. In eight cases dead tissue or foreign bodies were present. In 15 cases sinus tracts or scar tissue of other origins represented precisely the kind of tissue devitalized by trauma or sepsis or rendered avascular by sclerosis which cannot be sterilized by any known form of chemotherapy or antibiotic therapy.

Streptomycin apparently has its chief field of usefulness in acute infections complicated by cellulitis. When it was used for this type of infection in this series, complete resolution usually occurred without necrosis of the affected tissue and with satisfactory wound healing.

Streptomycin also has a field of usefulness in the therapy of acute gram-positive coccal cellulitides which are penicillin-resistant. Streptomycin also may be employed in the occasional case of gram-positive coccal infection in which the patient has developed a penicillin-sensitivity reaction. In the small number of cases in this series which fell into these categories the results were generally good. Streptomycin is probably even more useful in mixed infections in which the response to penicillin alone is not satisfactory because some organisms present are not penicillin sensitive and may, in fact, exert an actual penicillin-destructive effect.<sup>8</sup>

It is considerably more difficult to define the usefulness of streptomycin applied topically in localized infections with cellulitis. Some cases in this series improved under this form of treatment but the results were not dramatic in any instance. The impression was frequently received that the patients would probably have fared as well if streptomycin had not been used. Moreover, even in the improved cases, it was not possible to attribute the good results to streptomycin alone. They might equally well have been attributed to the mechanical clearing effect of improved drainage, or to combined surgical-antibiotic therapy. The results, in fact, seem to suggest that if local wound suppuration is not completely controlled within a period of 72 hours after the topical application of streptomycin is begun, the interpretation is warranted that whatever other function the local dressings may be fulfilling, their effect is probably not bacteriostatic.

Even when all the conditions set down for the proper use of streptomycin are met, it still does not follow that streptomycin therapy is the method of

choice in a given case. This is an extremely expensive drug. It is, moreover, an agent which is not free from risk, the optimum therapeutic dose, as has been pointed out, apparently being dangerously near to the critically toxic level. It therefore should be used in the type of case in which its usefulness has been established, only if no other drug will answer the purpose equally well. In the greater majority of cases penicillin will be equally effective. A distinction should be made, in other words, between cases in which streptomycin is indicated and cases in which it is mandatory. Available statistics seem to indicate that the cases in the mandatory category are not more than one in every 85.

Precise clinical standards do not exist for the ready selection of cases in which streptomycin is mandatory. For the present, the most that can be said is that it probably should be used:

(1) In mixed gram-positive and gram-negative infections in which clinical experience has shown that the results of penicillin therapy tend to be inconstant.

(2) In gram-positive infections in which there has been no response to maximal doses of penicillin within 48 to 72 hours, or earlier, if in vitro evidence of penicillin resistance can be secured.

(3) Generally speaking, in infections below the diaphragm, where gram-negative infections and mixed infections occur predominantly. Reclassification of this series of cases according to bacteriology made clear that infections of this origin were infrequent above that level. This is a practical point which may be of assistance if laboratory facilities are not readily available.

(4) In an occasional case, in the form of topical applications, to remove bacteria, in conjunction with a surgical procedure designed to eliminate dead or sloughing tissue. It should be remembered that the mere presence of gram-negative organisms in an infection of long duration is not per se an indication for streptomycin therapy. They are probably present as part of the evolution of the bacteriology of the wound, and until dead tissue is removed, streptomycin cannot be expected to be effective against them.

When streptomycin is used, it must be given in adequate dosage. The optimal dose, when it is used alone, is 2 to 3 Gm. daily, the duration of treatment depending upon the response. If treatment is discontinued too soon after a favorable response is apparent, recurrence is likely. On the other hand, if therapy must be continued longer than 14 days, the dosage should be reduced, to avoid the risk of labyrinthine disturbances.

The optimum dosage of streptomycin in combination with penicillin has not yet been worked out. From present indications it will be considerably less than the 2 to 3 Gm. daily now regarded as optimum when streptomycin is used alone. Probably it will not be more than 1 to 1.5 Gm. daily, given intramuscularly in 0.25 Gm. doses every four hours, in combination with 50,000 units of penicillin every four hours by the same route. Investigations to establish this point are currently being conducted.

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# PENICILLIN IN THE POSTOPERATIVE TREATMENT OF PEPTIC ULCER WITH PERFORATION AND APPENDICITIS WITH PERFORATION\*

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THIS REPORT is based on a study of the 42 cases of perforated peptic ulcers and 97 cases of perforated appendices operated at the Philadelphia Naval Hospital during the eighteen month period between January 1, 1946, and June 30, 1947. Patients from the Veterans Administration and active duty personnel are included in the series. Since the vast majority of these cases were surgical emergencies, operation was performed by the surgical watch officer. This officer is usually a younger surgeon with experience comparable to that of a surgical resident or younger staff man in a civilian hospital. There has been no rigid standardization of surgical procedure, the details of which have varied somewhat with the individual operator.

On the other hand the postoperative care in this series has been quite uniform throughout for each of the two groups of patients. In practically all of these cases the same ward medical officer supervised this care. With few exceptions, which will be noted, penicillin was administered postoperatively. Although some of the cases treated early in 1946 and an occasional case treated later received a smaller dosage of penicillin, 100,000 units every two hours became the accepted initial postoperative dose.

Penicillin in this dosage for appendicitis was suggested by Crile and Fulton.<sup>1</sup> Whether one subscribes whole-heartedly to the theoretical considerations upon which they based their use of relatively large doses of penicillin, one is forced to admit that their results in 1500 appendectomies, both from the standpoint of morbidity and mortality, are enviable.

In the past few years many reports on the treatment of perforated peptic ulcer and acute appendicitis with or without perforation have been published. Improved results have been attributed to chemotherapy and antibiotics alone or in combination with various operative and postoperative factors. Baritell<sup>2</sup> reports 88 perforated gastroduodenal ulcers operated in three years with one death (1.1%). He describes his operative and postoperative routine in detail which includes sulfadiazine intravenously and orally. No penicillin was used. The commonest complication in this series was wound infection (10.2%).

Thompson and Prout<sup>3</sup> in an article on the surgical treatment of peptic ulcer include 100 cases of acute perforation. Chemotherapy was used in 91% and penicillin in 14%. The mortality rate was 15%, and 34% of the patients

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developed wound infections. Estes and Bennett<sup>4</sup> operated upon 80 cases of perforated gastroduodenal ulceration. Their mortality rate was 8.7%. They attributed this relatively low rate to early surgical intervention, use of spinal anesthesia, immediate postoperative use of plasma, glucose, saline and sulfonamides.

Graham and Tovee<sup>5</sup> report their experience with 114 cases of perforated duodenal ulcer, 111 of which were treated surgically. The postoperative mortality rate was 6.3%. They emphasize the importance of preoperative treatment, even to delaying operation up to twelve hours. They decry the use of intraperitoneal sulfonamides.

Stafford, Beswick, and Deeb<sup>6</sup> reviewed 903 cases of acute perforative appendicitis. They found that with increasing use of sulfonamides the mortality rate decreased from 9.2% in 1939 to 3.4% in 1942. They conclude that the sulfonamides are effective in the treatment of peritonitis and of particular value when implanted intraperitoneally in the early stages. Newell<sup>7</sup> operated upon 48 cases of suppurative appendicitis with free pus in the peritoneal cavity. There were no deaths. In all cases 5 Gm. of sulfanilamide powder were placed in the peritoneal cavity which was not drained. Penicillin was used in large dosage in 11 cases.

Farkas<sup>8</sup> analyzed 648 cases of acute appendicitis treated surgically. Sulfonamides were given orally or intravenously to patients with evidence of peritonitis. Mortality rate was 1.65%, all deaths occurring in the group with perforated appendices and generalized peritonitis.

Ochsner and Johnston<sup>9</sup> compared results of treatment of patients with perforated appendices admitted to Charity Hospital in 1933 with those admitted in 1943. In 1933 the mortality rate was 15%. In 1943 it was 5.2%. The improvement is attributed not only to use of sulfonamides, but also to the administration of large amounts of blood and plasma, the employment of gastro-intestinal decompression, and the use of oxygen.

Mueller<sup>10</sup> in 1945 reported his experience with 739 cases of appendicitis in which local sulfonamides had been used in 320 instances. Penicillin was used postoperatively in the cases with abscess or peritonitis. Mortality rate was 0.4%. In a group of 742 treated prior to the use of chemotherapy and antibiotics, the mortality rate was 2.83%.

Experimental evidence points to the value of penicillin in the treatment of intraperitoneal infection. Fauley, Duggan, Stormont, and Pfeiffer<sup>11</sup> produced peritonitis in dogs by ligating the appendiceal base and blood supply. The mortality in 27 untreated controls was 92.7%. Of 48 dogs which were treated with penicillin and which did not develop fecal fistulae none died. If fecal fistulae did develop the animal died in spite of penicillin therapy. Harper and Blain<sup>12</sup> isolated jejunal loops in dogs. Fifteen control dogs died within 6½ days. Fifteen dogs receiving penicillin in the closed loop and five receiving penicillin parenterally were protected for significantly longer intervals. Their evidence showed that penicillin given prophylactically in large doses can

prevent infection of the distended intestinal wall by normal intestinal bacteria.

We are presenting our experience with large dosage of penicillin in the postoperative treatment of perforative appendicitis and perforated peptic ulcer not with the idea of attributing the results obtained to the antibiotic agent alone. We have neither sufficient clinical nor bacteriologic control data to justify such a conclusion. Use of penicillin was an integral part of a routine postoperative regime (Tables I and II), which we feel has contributed to the relatively low mortality and morbidity in each of the two groups of cases. It is hoped that this report may add to the accumulating data in the literature on the value of penicillin in intraperitoneal infections; data which will ultimately yield groups of sufficient size for critical breakdown and analyses of statistical significance.

TABLE I.—*Postoperative Routine—Perforated Ulcers*

1. 100,000 u. penicillin q. 2 hr. = initial dosage level.
2. Wangenstein suction drainage—usually continued 48-72 hrs.
3. Intravenous fluids as indicated: (blood, plasma, serum albumen, amigen, glucose, saline).
4. Ascorbic acid and thiamin chloride parenterally until oral feeding started
5. Modified Sippy Diet—after Wangenstein drainage discontinued.
6. Early ambulation in the absence of signs and symptoms of peritonitis.

#### PERFORATED PEPTIC ULCER

In this group there are 42 patients. Since the majority of these patients are veterans the associated factors commonly accepted as important in evaluating therapeutic results approach those of a civilian group except for sex distribution.

The ages of the patients ranged from 19 to 59. Nearly half of the perforations occurred in the third decade. Age distribution for the whole group is shown in Table III. The two patients who died were 27 and 29 years old.

TABLE II.—*Postoperative Routine—Perforated Appendices*

1. 100,000 u. penicillin q. 2 hr. = initial dosage level.
2. Wangenstein suction drainage in all cases of spreading peritonitis and in others with distension, vomiting, etc.
3. Intravenous fluids as indicated: (blood, plasma, serum albumen, amigen, glucose, saline).
4. Ascorbic acid and thiamin chloride—parenterally or orally.
5. Diet as tolerated.
6. Early ambulation in the absence of signs and symptoms of peritonitis.

In all but one case the time of perforation was established by the typical acute onset of severe, "doubling up," epigastric pain. Twenty-four (57%) of the patients gave a history or had had studies and treatment which justified the diagnosis of peptic ulcer prior to perforation. Several of the remainder of the group had a few days to weeks premonitory symptoms, but no definite previous attack or diagnosis. The time interval between perforation and operation is recorded in Table IV. Only 6 (14%) of the group were operated under six hours. Twenty-four (57½%) received their surgery in less than 12



hours. Two were over 24 hours and two more over 48 hours in duration. The two deaths occurred in patients whose ulcers had perforated 15 hours and 62 hours before operation.

The admission temperatures, pulse rates, and leucocyte counts were studied with the following findings: Temperatures ranged from 97 to 102, but in the vast majority of instances the preoperative temperature was below 100. On the other hand the pulse rate was more strikingly elevated, being over 100 in approximately half of the cases. In all cases the leucocyte count was over 10,000, and in half of the cases over 20,000 with a polymorphonuclear increase and shift to the left.

TABLE III.—*Age Distribution—Perforated Ulcers*

Years	No. of Cases	Per Cent of Group
Under 20 .....	1	2.4
20 - 30 .....	19	45.2
30 - 40 .....	7	16.7
40 - 50 .....	7	16.7
Over 50 .....	8	19.0

Roentgenologic examination for free air in the peritoneal cavity was made in 27 instances (64%). Air was demonstrated in 17 (63%) of those so examined.

An attempt has been made in Table V to classify the perforations as to location, but anyone familiar with this type of surgery realizes the difficulty of sharply localizing the lesion when landmarks are obscured by oedema.

TABLE IV.—*Duration of Perforation—Ulcers*

Hours	No. of Cases	Per Cent of Group
0 - 6 .....	6	14.3
6 - 12 .....	18	42.9
12 - 18 .....	9	21.4
18 - 24 .....	1	2.4
24 - 48 .....	2	4.8
48 - 72 .....	2	4.8
Not Recorded .....	..4	9.4

induration, and exudation. About one-third of the perforations were listed in the operative report as gastric, about one-third as duodenal, and a final third were simply reported as pyloric. In two cases the lesions were marginal or rather jejunal in location.

Details of operative technic will not be discussed except for a few brief notes. Spinal anesthesia was employed in all but one instance. The exception received ether and was one of the patients who died. An upper right rectus incision was used most frequently with an occasional transverse incision as the operator's choice. One jejunal perforation was operated upon through a left subcostal incision. All of the perforations were treated by simple closure with or without a reinforcing tab of omentum. Sulfonamides were used locally in 13 cases; 5 grams of sulfanilamide being the usual dose. All abdominal wounds were closed in layers but suture material varied to include catgut, cotton, and wire.

Thirty-one cases (74%) were drained. In analyzing the drainage cases

for an indication the following facts are revealed: In six of the 11 cases the interval between perforation and operation was over 12 hours. In these six cases are included the two who died, one of whom had a full blown peritonitis at operation 62 hours after perforation, and the other a tremendous amount of gastric content in the peritoneal cavity. Culture of the fluid from this latter case revealed hemolytic streptococcus and pneumococcus. In two other cases the operator notes that there was a considerable amount of free peritoneal spillage. In the remaining three cases there was no obvious reason for draining other than the surgeon's choice.

TABLE V.—*Location of Perforated Ulcers*

Classification	No. of Cases	Per Cent of Group
Gastric .....	12	28.6
Duodenal .....	12	28.6
Pyloric .....	15	35.6
Jejunal .....	2	4.8
Not Recorded .....	1	2.4

All patients in this group received penicillin postoperatively. In 34 cases the initial dosage was 100,000 units every two hours. Dosage was continued at this level for varying lengths of time up to 18 days in one patient. The average duration at this level was 8.5 days. Penicillin was then tapered off through decreasing dosage before being discontinued. Four cases received an initial dosage of 50,000 units every three hours and the remaining four a still smaller dosage. Both deaths occurred in the smaller dosage group

TABLE VI.—*Postoperative Complications—Perforated Ulcers*

Type	No. of Cases	Per Cent of Group
Pulmonary .....	5	11.9
Wound .....	2	4.8
Peritonitis (fatal) .....	1	2.4
Pelvic Abscess .....	2	4.8
Duodenal Fistula .....	1	2.4
Uremia (fatal) .....	1	2.4

before the 100,000 units every two hours was established as a routine. In two cases, including the death from peritonitis, sodium sulfadiazine was given intravenously in the first 24 hours in 5 Gm. dosage.

Postoperative complications are listed in Table VI. An uneventful convalescence was enjoyed by 32 patients (76%). There were three cases of transient atelectasis, one of the right lower and two of the left lower lobe. All cleared uneventfully. There was one case of bronchopneumonia in a patient with a ruptured jejunal ulcer who had in addition a disruption of his left subcostal wound. This was not accompanied by evisceration. The wound was packed, strapped and allowed to heal by granulation. The only other wound complication was a hematoma in the upper end of a right rectus incision. There were two complicating pelvic abscesses which subsided following spontaneous rupture into the rectum. One of these patients with a pelvic abscess also had a pneumonitis. The most serious and troublesome complication of all was a duodenal fistula. This fistula closed spontaneously but only after three weeks of supportive treatment which included jejunal feeding through a Miller-Abbott tube.

Two of the patients in the series died; a mortality rate of 4.8%. In the first instance the perforation was 62 hours old and the patient was critically ill on admission. After much controversy operative treatment was elected. Widespread peritonitis was found. The patient died of overwhelming infection 40 hours after operation. The second case was that of a 15-hour-old perforation in a mild diabetic who died in uremia 22 days after operation.

TABLE VII.—*Age Distribution—Perforated Appendices*

Years	No. of Cases	Per Cent of Group
Under 20 .....	9	9
20 - 30 .....	54	55
30 - 40 .....	19	20
40 - 50 .....	3	3
Over 50 .....	12	13

## ACUTE APPENDICITIS WITH PERFORATION

During the eighteen month period covered by this study 815 appendectomies were performed. In 166 cases (20%) the appendix was not acutely inflamed. In 552 instances (68%) the appendix was acutely inflamed or gangrenous but not perforated. In the remaining 97 cases (12%) a diagnosis of acute appendicitis with perforation was made. It is with this latter group of perforated appendices that this report is primarily concerned.

TABLE VIII.—*Duration of Symptoms—Perforated Appendices*

Days	No. of Cases	Per Cent of Group
1 or less .....	31	32
1 - 2 .....	19	20
2 - 3 .....	14	14
3 - 4 .....	3	3
4 - 5 .....	6	6
5 - 6 .....	2	2
6 - 7 .....	7	7
Over 7 .....	15	16

As with the ulcer group, certain factors considered important in prognosis and treatment will be discussed. Ages ranged from 16 to 73 with approximately half of the patients in the third decade of life (Table VII). A study of the time elapsing from the onset of symptoms to operation is summarized in Table VIII. It was interesting to find that perforation had occurred in as short a time as four to five hours and in 31 of the cases (32%) in less than one day. On looking for factors which might have contributed to appendiceal perforation it was found that at least 29 patients (30%) had taken cathartics, enemas, or both, prior to admission to the hospital. In four instances the laxatives were prescribed by physicians. In seven cases patients had been seen by an outside physician without the correct diagnosis being suspected and with resultant delay in treatment.

A study of the preoperative temperatures, pulse rates, and leucocyte counts showed that in 63 cases (65%) the initial temperature was over 100, but in only 36 patients (37%) was the pulse rate that high. This picture is quite different from that of the ulcer group. The difference is a predictable one, however, when one considers that the relatively low temperature and rapid

pulse rate of the ulcers is a reflection of the more severe peritoneal irritation commonly associated with that type of perforation. The leucocyte counts in the appendicitis group ranged from 6,400 to 29,400 with 62 (64%) of the counts between 10,000 and 20,000.

Spinal anesthesia was used in all 97 cases. The abdomen was entered through a right lower quadrant muscle splitting incision in 70 patients, a right rectus incision in 23, and in three instances the type is not recorded in the operative report. An inguinal incision was used in one case in which the appendix had perforated into a right indirect inguinal hernial sac and in which the preoperative diagnosis was strangulated hernia.

In Table IX the cases are listed according to the type or extent of intra-peritoneal infection associated with the appendiceal perforation. In 18 (19%) of the cases a generalized or perhaps better termed, a spreading peritonitis was found. In 23 (24%) the process was apparently localized. In 37 instances (38%) a true abscess was found and in 10 cases contamination was due to rupture of the appendix during its removal. Appendectomy was performed in 78 cases (80%).

TABLE IX.—*Associated Intra-peritoneal Infection—Perforated Appendices*

Classification	No. of Cases	Per Cent of Group
Generalized Peritonitis .....	18	19
Localized Peritonitis .....	23	24
Abscess .....	37	38
Contamination due to perforation on removal .....	10	10
Not accurately recorded.....	9	9

Local antibiotic or chemotherapy, usually 5 Gm. of sulfanilamide, was used in 71 patients (73%). In two instances 100,000 units of penicillin was instilled locally. Of the cases in which this local therapy was not practiced, nine were abscesses, 12 local or spreading peritonitis, and five were appendices ruptured during removal.

Seventy cases (72%) were drained. Drainage was usually by Penrose or cigarette drains to the appendiceal site. Drains were placed also in the right lateral gutter and pelvis in several cases in which these latter areas were actually or potentially infected. The majority of undrained cases were those with local or spreading peritonitis or those in whom the appendix had been ruptured during removal. Only two abscesses were closed without drainage.

Cultures taken at operation add little to the study, with *E. Coli* the predominant organism throughout.

In 71 (73%) of the patients penicillin was administered at an initial dosage level of 100,000 units every two hours. The duration of treatment at this level ranged from one to 26 days with an average of 5.3 days. Twenty of the group received smaller initial dosages of penicillin postoperatively. Six patients in whom contamination of the peritoneal cavity was minimal, including three with appendices ruptured during removal, received no penicillin postoperatively. Twelve of the group were treated with 5 Gm. of sodium sulfadiazine intravenously in addition to the postoperative penicillin.

Complications are listed in Table X. The incidence of pulmonary complications is very low (1%) with only one case of transitory atelectasis. Infection occurred in two McBurney incisions which were not drained and in three right rectus incisions associated with drainage through a stab wound. Pelvic abscesses developed in six cases. Three required surgical drainage and three perforated or subsided spontaneously. Three of the six were diagnosed as a localized peritonitis at the original operation, one as a spreading peritonitis, one an abscess, and in one case the appendix was ruptured during removal. All had received sulfanilamide locally; three had been drained and three not drained.

There were two postoperative gastro-intestinal hemorrhages in the group. One occurred as melena and gross hematemesis in a 73 year old man with widespread peritonitis. He bled down to an erythrocyte count of 1,300,000 before the hemorrhage ceased spontaneously. Studies including roentgenological examination of the gastro-intestinal tract during convalescence failed to reveal the source of the bleeding.

TABLE X.—*Complications—Perforated Appendices*

Type	No. of Cases	Per Cent of Group
Pulmonary .....	1	1
Wound .....	5	5
Pelvic Abscess .....	6	6
Thrombophlebitis .....	1	1
Penicillin Reaction (Urticaria)...	1	1
Gastrointestinal Hemorrhage .....	2	2

The second case of hemorrhage resulted in the only postoperative death, a mortality rate of 1% for the ruptured appendices, and 0.12% for the entire group of 815 appendectomies. This patient, an 18 year old male, had a perforated appendix with localized peritonitis. The appendix was removed and the crushed stump was inverted in the cecum without ligation. The patient died of a concealed massive intestinal hemorrhage on his fifth postoperative day. At autopsy the source of bleeding was found to be the unligated appendiceal stump. This unfortunate death must be attributed to this fortunately little used technic which increases the danger of just such a complication.

## COMMENT

It is our opinion, based on clinical impressions, that inclusion of penicillin therapy in our routine postoperative treatment of perforated peptic ulcers and perforated appendices has contributed measurably to the low mortality and low morbidity rates for the two groups. Complications due to spread of the existing infection or development of new infectious processes were almost entirely eliminated. In only one of the two ulcer deaths did infection play a part and this was an overwhelming peritonitis from the start. The one death from appendicitis was in no way related to infection. True, there were several residual pelvic collections in the two groups, but even some of these subsided spontaneously under continued penicillin therapy. Primarily infectious pulmonary complications were rare. The most noteworthy observa-

tion was the complete absence of wound suppuration in the ulcer group. This is in striking contrast to our past experience with these cases and to the incidence of wound infection reported by others.<sup>2, 3</sup>

It may justifiably be asked why we have not presented a control series with which to compare our data for a more accurate evaluation of the contribution of penicillin to our results. Such a series is not obtainable. Comparison with similar groups of cases treated at this hospital in the pre-penicillin era introduces too many additional factors which have been added to our routine postoperative regime. These include earlier ambulation and oral feeding, more intensive vitamin therapy, and an increasing use of whole blood plasma, serum albumen, and the protein hydrolysates.

#### SUMMARY

1. This report is based on 18 months experience with penicillin as an integral factor in the routine postoperative treatment of perforated peptic ulcers and perforative appendicitis.

2. Penicillin was given parenterally in large doses (usually 100,000 units) at short intervals and maintained at this dosage level for days or even weeks in those cases in which the slightest indication for continuation of therapy persisted.

3. In a group of 42 ruptured ulcers there were two deaths; a mortality rate of 4.8%. There were only two wound complications in the group, neither primarily infectious.

4. There were 97 perforated appendices in a total series of 815 appendectomies. There was one death; a mortality rate of 1% for the ruptured appendices and 0.12% for the entire group.

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# RESURFACING PROCEDURES IN COMPOUND INJURIES OF LOWER EXTREMITIES†\*

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IN THE RECENT WAR, military surgery of the extremities dealt with a great number of compound injuries. Most of them were the result of gunshot wounds, mine explosions, etc., and presented a kind of injury seen relatively infrequently in civilian life. These injuries were characterized by extensive destruction of all layers of tissue, both the superficial and deep structures, skeleton and soft tissues alike.

Improved methods of controlling infection and more efficient surgical management were responsible for preserving many severely damaged extremities which might otherwise have been sacrificed. To rehabilitate these extremities and restore them to a maximum of useful function was the task of specially designated Army hospitals. This was accomplished through the combined planning and work of the three reparative surgical specialties—orthopedics, neurosurgery, and plastic surgery.

The cases referred to the Plastic Surgery Section presented extensive deep scarring which was either unstable or in such a location that it precluded any essential surgery on the deep structures. Some cases had temporary skin grafts and others showed indolent ulcerations. In almost 50% of the cases which came to resurfacing, some sort of bone graft to correct nonunion was anticipated. Other procedures for which resurfacing had to be done were osteotomies for malunion, arthrodeses (often combined with bone grafts), tendon transfers, and nerve sutures. These operations required an adequate exposure of the involved structures, and their success depended largely on primary healing of the operative wound. Extensive scar tissue did not withstand such operative trauma. Furthermore, a bone or tendon graft or a nerve suture needed the protection of a well vascularized soft tissue pad and did not do well in a mass of avascular fibrous tissue.

The plastic surgeon's task was two-fold: to supply a stable and adequate tegumental layer and/or to create conditions favorable for major procedures on the deep structures.

The procedures used in accomplishing these ends were:

- 1) Free skin grafts
- 2) Flaps
  - a) Contiguous
  - b) Direct flaps from the opposite extremity, or
  - c) Distant flaps from the trunk

To plan the surgical treatment of the individual patient, the simplest possible method was selected which would fulfill the requirements of the case

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\* Cases from Cushing General Hospital.

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with a minimum of additional scarring and discomfort.

The main purpose of this discussion is to evaluate the relative merits of each method and its adaptability to specific problems. Since the standard technics are well known, only the fundamentals of the procedures and those modifications which were found to be of substantial assistance will be emphasized.



FIG. 1.—The split skin graft. (A) Extensive scarring and ulceration on anterior and lateral surfaces of distal portion of leg and foot as a result of gunshot wound. Comminuted fracture of the tibia and fibula drained for a prolonged period of time. However, fractures healed, and there was no roentgenographic evidence of bony infection. There was spontaneous fusion of ankle joint. (B) The whole scarred area was excised. Two bony cavities filled with granulations were encountered. They were curetted and packed. Defect was covered with split graft which was perforated over packing. Four weeks later when bone cavities were filled with firm granulations, two small split grafts were added. All grafts took well, and no further surgery was necessary.

#### FREE SKIN GRAFTS

The free skin graft of intermediate thickness offered the simplest and ordinarily a one stage procedure for treating compound injuries. However, it had a limited field of usefulness. While the grafts took well on a fibrotic base, in the presence of deep scarring, they adhered intimately to the underlying structures. In the absence of a soft tissue pad, particularly over bone, they remained unstable and had a tendency to form indolent ulcerations. They were used, however, in some instances where further exploration of the



area was not anticipated (Fig. 1). Occasionally they were combined with local flaps (Fig. 2). In such instances the flap was reserved for selected locations, like the denuded bone or tendons, the graft covering the surrounding area. Free skin grafts were used routinely with all extremity flaps to cover the secondary defect. Since there was a muscular pad under these donor sites, the grafts offered an adequate and stable cover.

Thin Thiersch grafts were used extensively for temporary resurfacing (Fig. 8A). They could be procured easily, and their source was almost unlimited. Early "skin dressing" of wounds which could not be closed by suture



FIG. 2.—Sliding flap combined with a split skin graft. (A) Extensive scarring and chronic ulceration over external malleolus. (B) Scar was excised and exposed bone was chiselled off. Denuded bone was covered with a posterior sliding flap. Posterior donor area as well as remaining anterior portion of defect was resurfaced with a split graft. In this case one procedure, a combination of contiguous flap and free graft, obviated the necessity of a large cross thigh flap which would require multiple stages and prolonged hospitalization.

was an established surgical principle. In the treatment of localized osteomyelitis, so frequent in gunshot wounds of the bone, temporary thin grafts were used after sequestrectomies or saucerizations, though it was apparent that in most of the cases more adequate resurfacing would ultimately be needed.

#### FLAPS

A flap was indicated wherever, in addition to the skin, a soft tissue pad was needed. This pad served to replace a mass of avascular tissue and became a protective as well as a vascularizing factor in its new location. Striking examples of this were cases of non-union where a healthy callus began to form as soon as the scar tissue between the fragments was replaced by a soft tissue pad.

Ulcerations or the presence of small granulating areas were not incompatible with the application of flaps. However, inflammatory reaction, drainage,

the presence of deep sinuses, or massive edema were contraindications for resurfacing with a flap. In such cases, temporary thin grafts helped to get the extremity in condition for further surgery.

In all cases of osteomyelitic infection, the flap was delayed for a few months after the drainage had ceased, so that a flare-up of the infection would be unlikely. The recurrence of infection underneath a flap leads to sinus formation, chronic drainage, fibrosis and shrinkage of the flap, and may necessitate a repetition of an involved procedure, besides wasting the most favorable source of the flap.

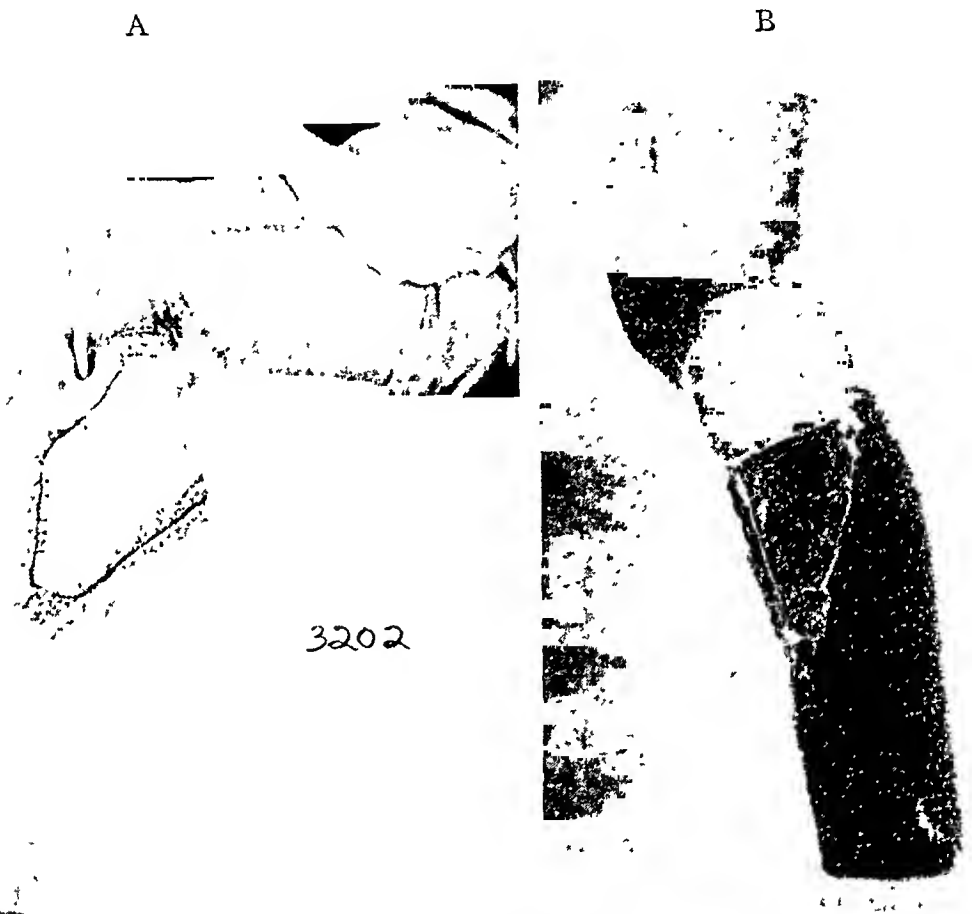


FIG. 3.—Rotation flap combined with iliac bone graft. (A) Post-osteomyelitic bony cavity in a proximal portion of the tibial shaft. Cavity had narrow opening and was completely epithelized with a thin Thiersch graft a few months previously. Surrounding skin was scarred. Delayed rotation flap based in the popliteal region. (B) After temporary skin graft was thoroughly removed and bony walls freshened, the cavity was filled with iliac bone chips. Surrounding scar was excised and replaced with the prepared flap. Donor area grafted.

Closure by approximation after excision of a scar was seldom possible. The size of the scar was often misleading. When the scar was excised and normal tension was restored, the borders of the wound retracted, often doubling or tripling the defect.

#### CONTIGUOUS FLAPS

A classical method of dealing with excessive tension is a relaxation incision. Such an incision, combined with complete undermining of the bridge of skin

between it and the defect, forms a bipediced sliding flap (Fig. 2). The sliding flap was particularly applicable to long, relatively narrow defects along the anterior border of the tibia. When the defect was more square or round, a rotation flap was indicated (Fig. 3). Such a flap had only one pedicle, acquired more mobility, and could adapt itself better to depressions and uneven surfaces. It could be rotated 30-120 degrees, as long as any strangulation of the pedicle was avoided.



FIG. 4.—Delayed cross thigh flap (A) Soft tissue loss along medial and anterior surface of mid-third of leg. Non-union of tibia with loss of substance. Adequate resurfacing was essential before a bone graft could be undertaken. (B) Flap on opposite thigh after two stage delaying (17 cm long and 12 cm wide).

Rotation flaps were based proximally or distally (retrograde). The latter, as well as the retrograde cross extremity flaps, did not exhibit any unusual difficulty of venous return (Fig. 5b, 5d).

The secondary defect, left by the sliding or rotation flap, was reduced by undermining the posterior skin edge, advancing it, and basting it down with a row of subcutaneous sutures. The remaining part of the defect was always skin grafted. Closure of the secondary defect was not attempted since it would place the flap under tension and so jeopardize its vitality.

The contiguous flap had the advantage of simplicity, limitation of surgery to the injured extremity, and avoidance of uncomfortable immobilization.

However, it could be used only when the skin around the defect was intact and a large enough flap could be obtained adjoining the defect. Furthermore, there were a great number of extensive injuries of the lower extremities, combined with non-union of the bone of the distal portion of the leg, where local flaps had a limited field of usefulness. In this location the blood supply was poor. Little skin and subcutaneous tissue was available under the best circumstances, and the secondary free graft was more vulnerable.

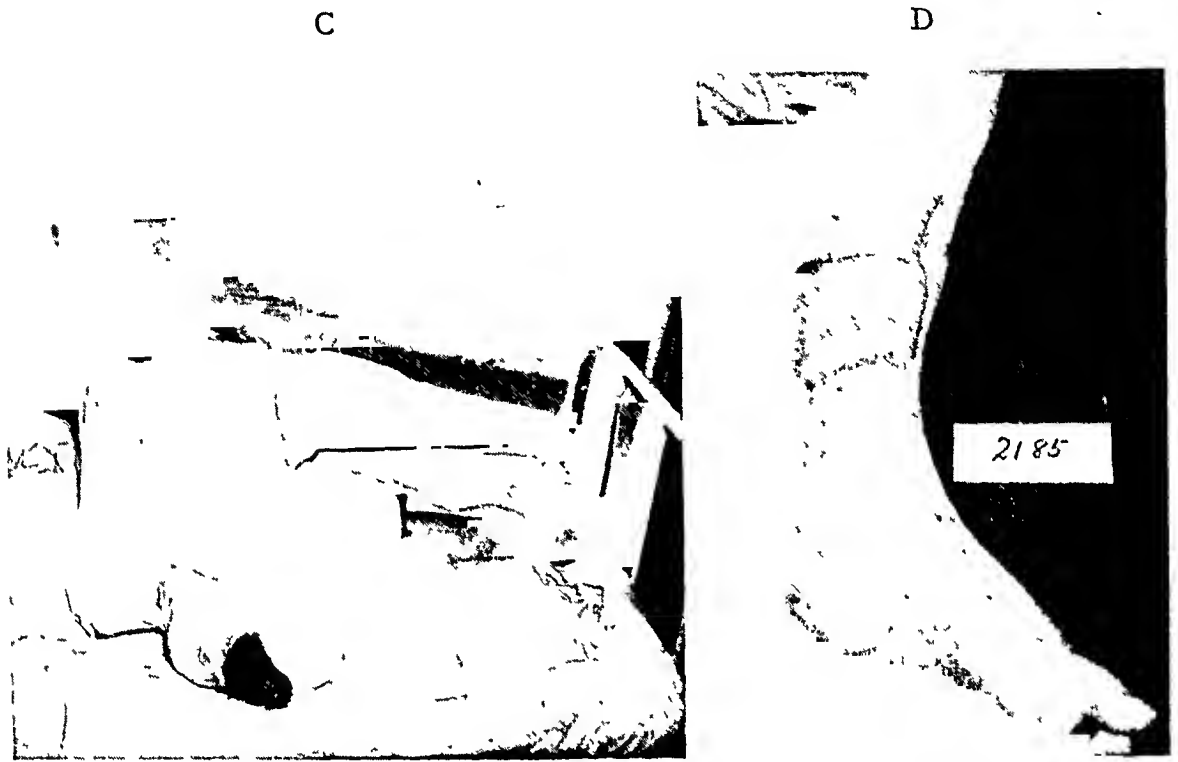


FIG. 4. (C).—Both extremities immobilized in plaster which was not changed or removed for three weeks until flap was to be severed. Window was made on twelfth day for inspection. Use of sulfanilamide powder over wound within the layers of gauze helped absorb secretion and eliminated decomposition. Patient usually required sedation for first 72 hours because of pain in flexed knee. There was little complaint thereafter. It was helpful to install a Balkan frame from which the extremities could be suspended. Patient could use trapeze to change position in bed by himself despite weight of plaster. (D) Flap set in.

#### CROSS EXTREMITY FLAPS

Whenever a contiguous flap of adequate size and thickness could not be obtained, the opposite extremity offered the next best choice as a source of flaps. In compound injuries of the distal two-thirds of the leg, the cross extremity flap was most frequently used. In our opinion a direct open flap, if it could be done according to the principles described below, was preferable to a tubed flap. Tubing and untubing of flaps and provisions for their transfer required planning for much larger flaps than the defect called for. The numerous stages would be time consuming and held the possibility of complications which might jeopardize the whole plan.

The tube was very helpful when a direct transfer was not feasible and when the flap had to be protected from shrinkage and infection during intermediate steps. Immediate skin grafting of the donor area and, if desired, of the undersurface of the pedicle eliminated the granulating surface or kept it to a minimum. With proper dressing technic, (Fig. 4c) maceration was avoided, the discharge controlled, and the postoperative care greatly simplified. Purulent infection was practically non-existent. (It is difficult to evaluate to what extent this was due to the routine use of sulfanilamides or antibiotics.)

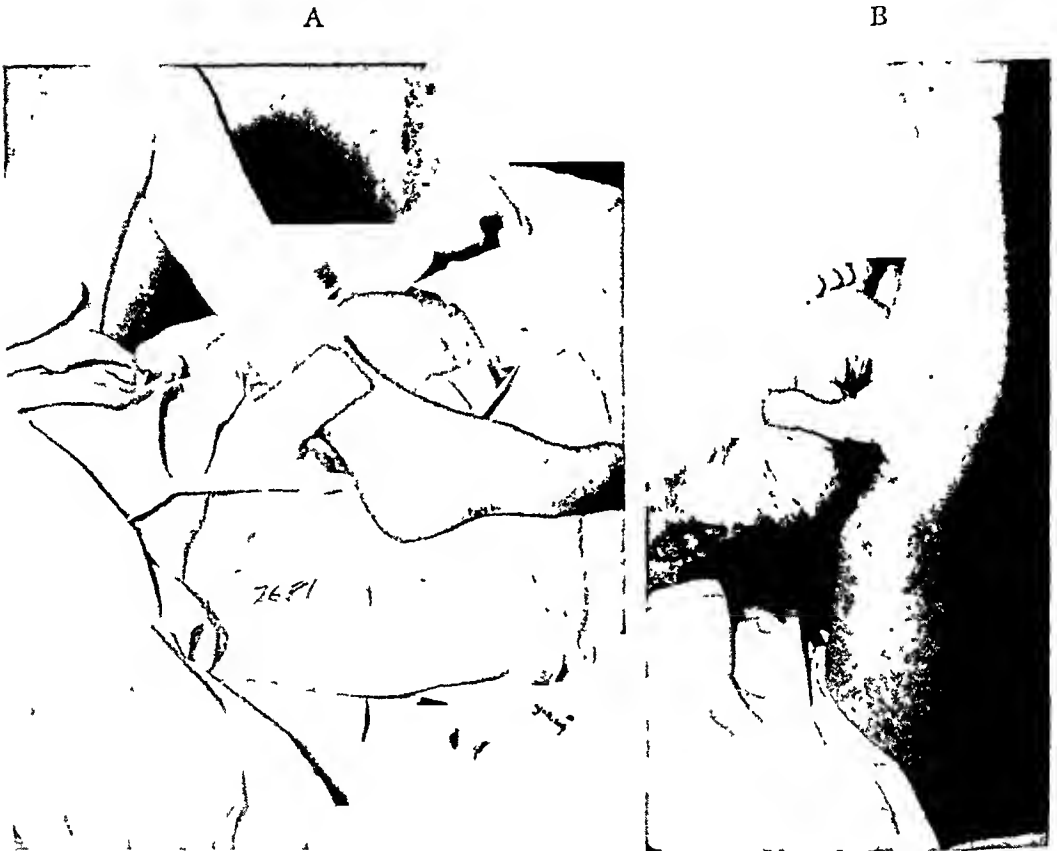


FIG. 5.—Undelayed cross thigh and cross leg flaps. (A) Defect along medial surface of tibia. Thigh flap 9 cm. long and 7 cm. wide for resurfacing of defect on medial surface of leg preparatory to bone graft for non-union. (B) Retrograde flap on medial surface of leg 10 cm. long and 7 cm. wide for resurfacing of extensive scarring and persistent fissure on sole of foot. Note that flap was allowed to contract in order to fill depth of defect.

In designing our flaps, the aim was always to keep the pedicle as wide as possible. The length of the flap was never more than one and one half times its width (Fig. 4). If feasible, the width of the flap exceeded its length (Fig. 5e). An attempt was always made to bring the recipient area into such approximation to the source of the flap, that the whole flap, or its major portion could be inserted at the first operation (Fig. 5). This plan limited the procedure to one major operation during which all the dissection was performed. It also assured an adequate blood supply to the flap after severance



FIG. 5. (C).—Oblique flap based along popliteal line 10 cm. long and 8 cm. wide to resurface fissure on heel. Heel was previously resurfaced elsewhere with a cross thigh flap. However, flap did not unite with skin on sole of foot, and a persistent fissure developed extending down to bone. (D) Retrograde flap from thigh 13 cm. wide and 12 cm. long for resurfacing of defect on anterolateral surface of leg. (E) Widely pedicled horizontal cross leg flap.

of the pedicle. The remaining steps were of a minor nature.

This procedure could be followed in the majority of our cross extremity flaps only by utilization of a variety of sites on the leg or the thigh. Medial, lateral and posterior surfaces of the proximal two-thirds of the leg and the

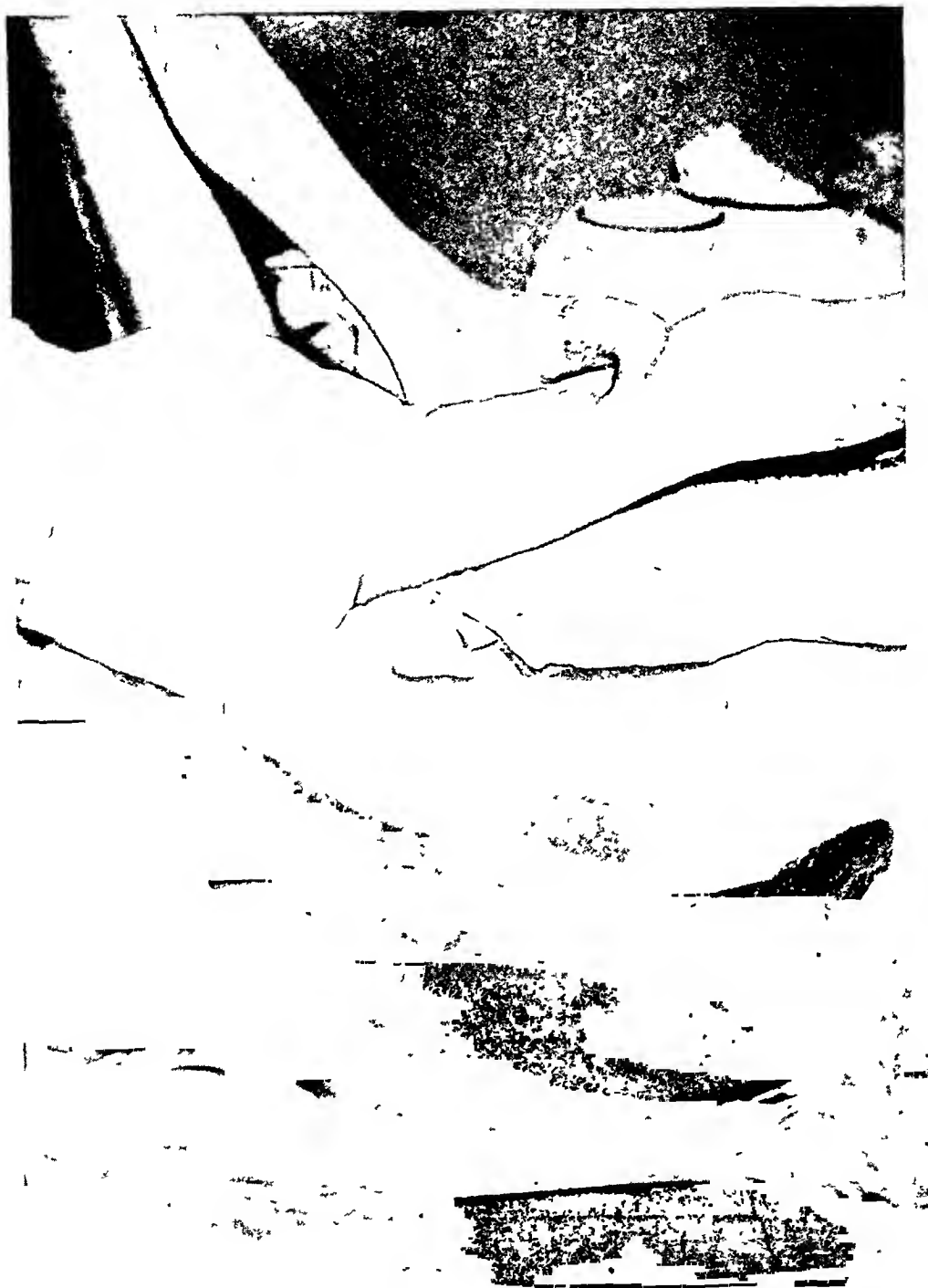
A



B

FIG. 6—Cross thigh and cross leg flaps for resurfacing of a bilateral deformity. (A) Amputation of all toes bilaterally as a result of frostbite Scarring and ulceration over forefoot. (B) Undelayed retrograde flap from medial surface of opposite leg was used for right foot.

C



D

FIG. 6 (C).—Retrograde undelayed cross thigh flap from anteromedial surface of thigh was used for left foot. Thigh site was preferred for left foot, because much larger flap was required to cover defect on this foot. Flap also had to cover a considerable portion of the plantar surface. Because of poor blood supply of the foot and the necessity of carrying about 50 per cent of flap for plantar surface, severance of flap was preceded by a delaying operation. (D) Final result: Skin grafted donor areas on right thigh and left calf. Note two small scars within flap on right, as a result of superficial ulceration.





FIG. 7.—Ill-advised flap. Delayed flap for resurfacing of a defect on the opposite leg, (done elsewhere). Note necrosis of tip. This flap was too long and narrow and extended too far distally.

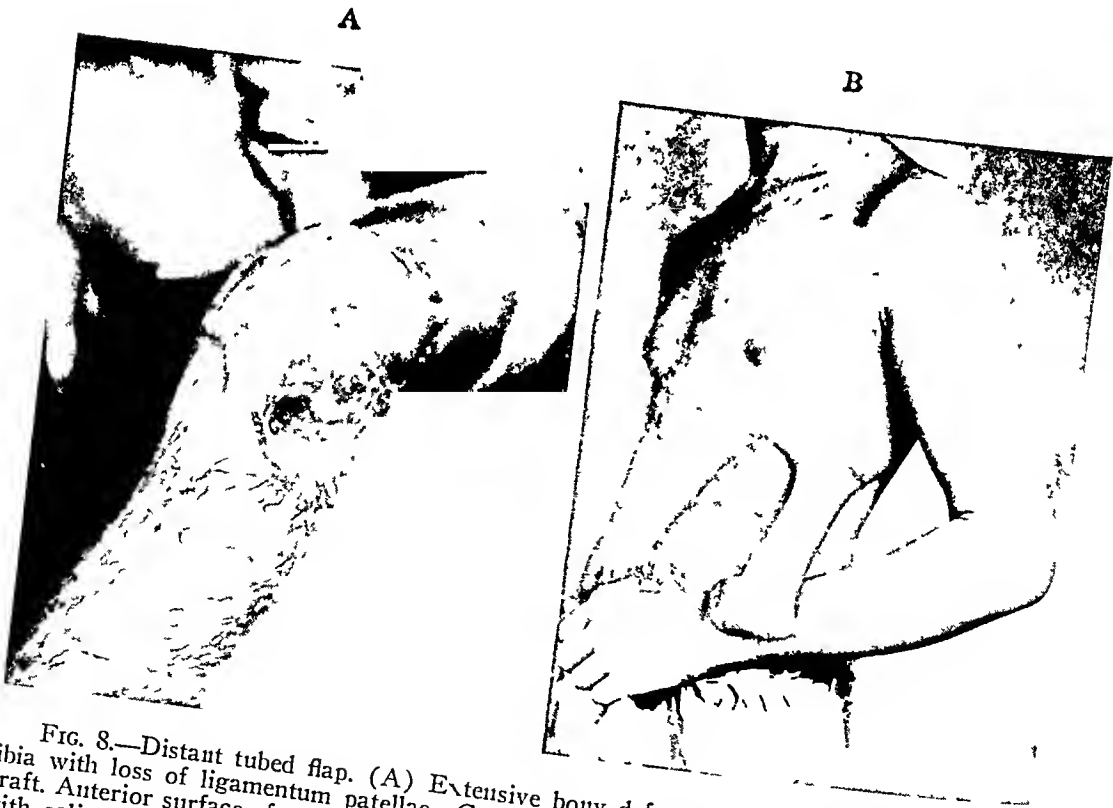


FIG. 8.—Distant tubed flap. (A) Extensive bony defect in the proximal shaft of the tibia with loss of ligamentum patellae. Cavity was covered with a thin temporary skin graft. Anterior surface of patellae and of distal portion of thigh was previously resurfaced with split graft. Knee motion greatly limited due to fibrous adhesions and scarring of quadriceps. (B) Thoraco-epigastric skin tube transferred to forearm. Tube 5" x 9". Note "trap-door" flap on forearm. It was reflected distally, thus doubling surface of attachment of flap. Proximal end of tube had already been delayed.

lateral and anterior aspects of the thigh were frequently used. The presence of a well developed fascia layer facilitated dissection and offered an excellent bed for the skin graft. Flaps were never cut across the popliteal space or along the anterior aspect of the leg where a skin graft would be vulnerable.

C



D

FIG. 8. (C).—Transfer of tube to knee region. Note wide attachment of tube away from scarred area in order to encourage revascularization of tube. (D) After final insertion of tube. This procedure required seven minor and major operative stages.

Experience demonstrated that most of the small or medium sized flaps did not need to be delayed (Fig. 5, 6b). However, when the flap was large or whenever there was any doubt about the adequacy of the circulation, delaying was essential (Fig. 4, 6c).

Rigid immobilization of the legs in plaster relieved the patient of any acute discomfort after the initial period of 48-72 hours (Fig. 4c). The less the knee was flexed the more comfortable was the immobilization. This consideration favored the use of leg flaps. On the other hand, there was less hesitation in removing large flaps from the thigh than from the leg.

All distant flaps must develop a completely new blood supply before they are detached from their original site. Therefore it was essential to excise all the scar tissue in order to allow the flap to join with healthy tissue. Very small flaps did not do well since they did not have an adequate opportunity to develop a new blood supply. Small defects were enlarged by allowing the surrounding skin to retract or, in some instances, by sacrificing normal skin.

The pedicle was severed in about three weeks. If the final insertion of the flap required any appreciable dissections, it was delayed for seven to ten days after the severance of the pedicle. Otherwise the circulation of the free portion of the flap might have been endangered.

Minor complications of cross extremity flaps were superficial ulcerations as shown in Fig. 6d, or delayed healing at the time of the insertion of the pedicle. These, however, did not jeopardize the results. Major complications, such as full thickness losses were very infrequent. Of 33 cases of cross extremity flaps, whose records were available for review, one case required an additional cross leg flap. The loss involved the proximal portion of a small flap when an attempt was made to insert it at the time of the severance of the pedicle. In two cases, small losses were replaced by local rotation flaps. In a few other cases, a revision of the scar was undertaken in preparation for a bone graft before the patient was referred to the orthopedic department for further surgery.

#### DISTANT FLAPS

In several instances neither a contiguous flap nor a cross extremity flap was applicable. The required flap was so large that it could not be taken from an extremity. Defects over the proximal part of the leg along the lateral surface could not conveniently be brought into close approximation with a satisfactory source of flap on the opposite extremity. The desirable donor areas were sometimes damaged in previous operations, or one of the opposite extremities might have been amputated. Removal of the flap from the amputation stump was hazardous, since the remaining skin graft might not withstand the friction and pressure from the bucket of the artificial limb. In cases of ankylosis of the knee joint in the involved extremity, a cross leg flap could rarely be used. In all these instances, a distant flap from the trunk was indicated. It was our opinion that this method should be used only as a last resort, since it required multiple stages, considerable time, and subjected the patient to uncomfortable immobilization.

The tube flap offered the safest and most convenient form for transferring tissue from a distance. When the flap was of moderate size, an oblique abdominal tube was formed which allowed for primary closure of the donor

area. When large tubes were needed, the thoraco-epigastric variety was preferred, and the underlying surface on the abdomen and chest was skin grafted. The tube was then attached to the distal portion of the forearm for migration into its new location. The management of such a case is shown in Figure 8.

In the majority of our cases the resurfacing completed only one phase of the treatment. It was the orthopedic surgeon who most frequently took further responsibility for the rehabilitation of the patient. The plastic surgeon remained available to advise on the precautions necessary to safeguard the flap and to assure primary healing after the operation on the deep structures.

Many of the subsequent complications following bone grafts, arthrodesis, etc. could be traced back either to an inadequate flap or to ill-planned incisions and exposures in the presence of a satisfactory flap. Close cooperation between the specialties produced better understanding of each other's problems and helped to avoid many of these complications.

#### SUMMARY

The importance of adequate resurfacing in the rehabilitation of compound injuries of the lower extremities is emphasized. Several procedures are described with particular attention to their comparative merits and limitations in meeting the requirements of individual cases. Skin grafts, contiguous flaps and flaps from the trunk are discussed. Since the cross extremity flap was most frequently used as a preliminary to further orthopedic procedures, its design and essential points of technic are elaborated.

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invasion has occurred. This is of much greater importance in the male, for the interposition of the uterus together with the broad ligament and ovaries in the female renders vesical invasion from colonic malignancy less likely.<sup>3</sup> Where bladder invasion is found either at cystoscopy or during operation, the location of the invaded area will determine whether the situation is "operable" or not. When the dome of the bladder, or its posterior wall is involved, partial resection of the bladder may be performed and the bladder closed preferably about a cystostomy tube, although often the surgeon is able to close the bladder completely, providing urinary drainage via a catheter placed urethrally. Any procedure wherein a portion of the bladder is resected necessarily adds to the operative risk.

Carcinomatous invasion of the trigonal area of the bladder, the prostate or seminal vesicles produces in most cases an "inoperable" condition and removal of the bowel malignancy is generally impossible. However, it is entirely possible that more radical surgery will make these cases "operable"; abdominoperineal resection of the rectosigmoid together with total cystectomy and removal of the prostate and seminal vesicles may be performed. In such a situation, of course, it would be necessary to transplant both ureters to the left colon above the site of resection. This indeed would be a formidable surgical attempt, but no doubt will be performed frequently in due time.

Deliberate bladder surgery in cases of malignancy of the rectosigmoid, however, is totally different from the inadvertent injury to the bladder wall which may occur incidental to the operative procedure on the colon. In the latter instances, a suture may accidentally be taken through the bladder wall; with subsequent necrosis of the tissue involved in the suture, a small opening appears in the posterior vesical aspect and urinary drainage reveals itself in the wound. Such drainage occurs approximately 10 to 14 days postoperatively and where the bladder defect is not a huge one, conservative management is indicated and spontaneous healing of the urinary fistula occurs. The bladder must be kept in a contracted state, and the urine diverted for a minimum of two weeks following appearance of the urinary drainage. Differentiation of vesical drainage from ureteral fistula must, of course, first be made by urography and cystoscopy.

In our series of 15 cases of urinary complications occurring in 100 operations for left colon malignancy, there was one instance of inadvertent bladder injury with resultant vesicoperineal fistula; spontaneous healing occurred with conservative management.

**Case 2.** PGH No. J-80224. A 63-year-old gardener complained of frequent bloody stools of 3 months' duration. A mass was felt at the tip of the rectal examining finger. Biopsy revealed the mass to be adenocarcinoma of the rectum. A preliminary colostomy was performed, followed one month later by abdominoperineal resection of the rectosigmoid colon. At operation, there was no apparent extracolonic spread of the carcinoma, and no difficulties were encountered in removing the colonic segment. Twelve days following the latter operation, clear urinary drainage appeared from the posterior wound several days after the patient was voiding without difficulty. Intravenous urography was

performed, and the cystogram disclosed urinary drainage from the left lateral superior border of the bladder (Fig. 2). An indwelling urethral catheter was relied upon for constant bladder drainage, and intermittent bladder lavage was performed. No further urinary drainage from the perineal wound was noted, and 18 days after discovery of the vesico-perineal urinary drainage, the urethral catheter was removed with no subsequent drainage or other urinary problem.

#### VESICAL DYSFUNCTION

Probably the most distressing and certainly the most frequent urinary complication after pelvic colon surgery is the problem of the bladder which is unable to empty itself and/or which becomes infected. Twelve of the 15 cases in our series were of this character; these cases ranged from severe upper urinary tract infection to serious symptoms of cystitis accompanied by urinary retention and, in four cases, another operative procedure, namely transurethral resection of the prostate had to be performed before "cure" could be accomplished.

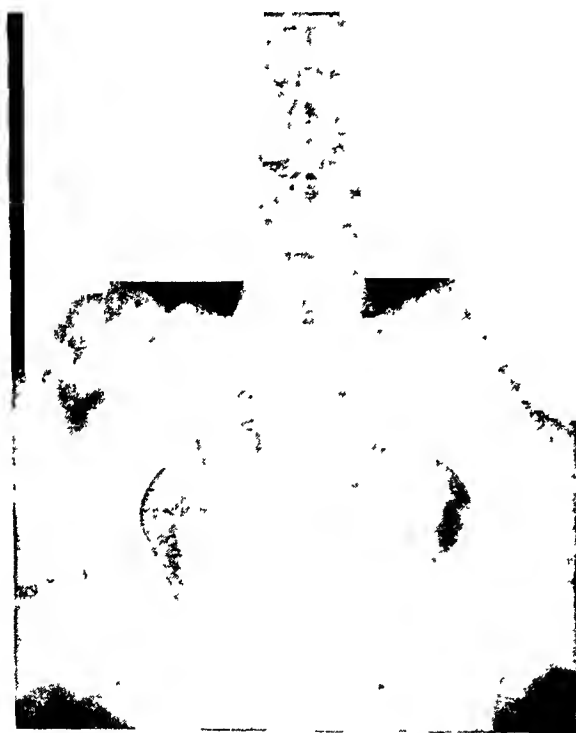


FIG. 1.



FIG. 2.

FIG. 1. Case 1.—Obstruction to passage of catheter in ureter and extravasation of contrast substance indicating ureteroperineal urinary fistula.

FIG. 2. Case 2.—Cystogram disclosing extravasation of contrast substance from defect in cephalad aspect of bladder.

The majority of these cases occurs where perineal dissection is performed and in males (in our series of bladder dysfunction, 9 out of the 12 patients were male). The reason for the preponderance of males will be seen in the discussion below. The most prevalent theory for explanation of bladder dysfunction is that of injury to the autonomic nervous system during mobilization and excision of the distal colon. Undoubtedly this factor plays an important role in the inability of the bladder to empty itself postoperatively, but one cannot

ascribe the entire cause to this single factor. Other important etiologic elements are: (1) direct trauma to the bladder, (2) prostatic obstruction, and (3) post-operative sagging of the bladder. It is our belief that no one element can be singled out as *the* cause of the bladder dysfunction seen in these patients, and that all in concert, perhaps with one factor more prominent than the rest, act to prevent normal bladder function postoperatively:

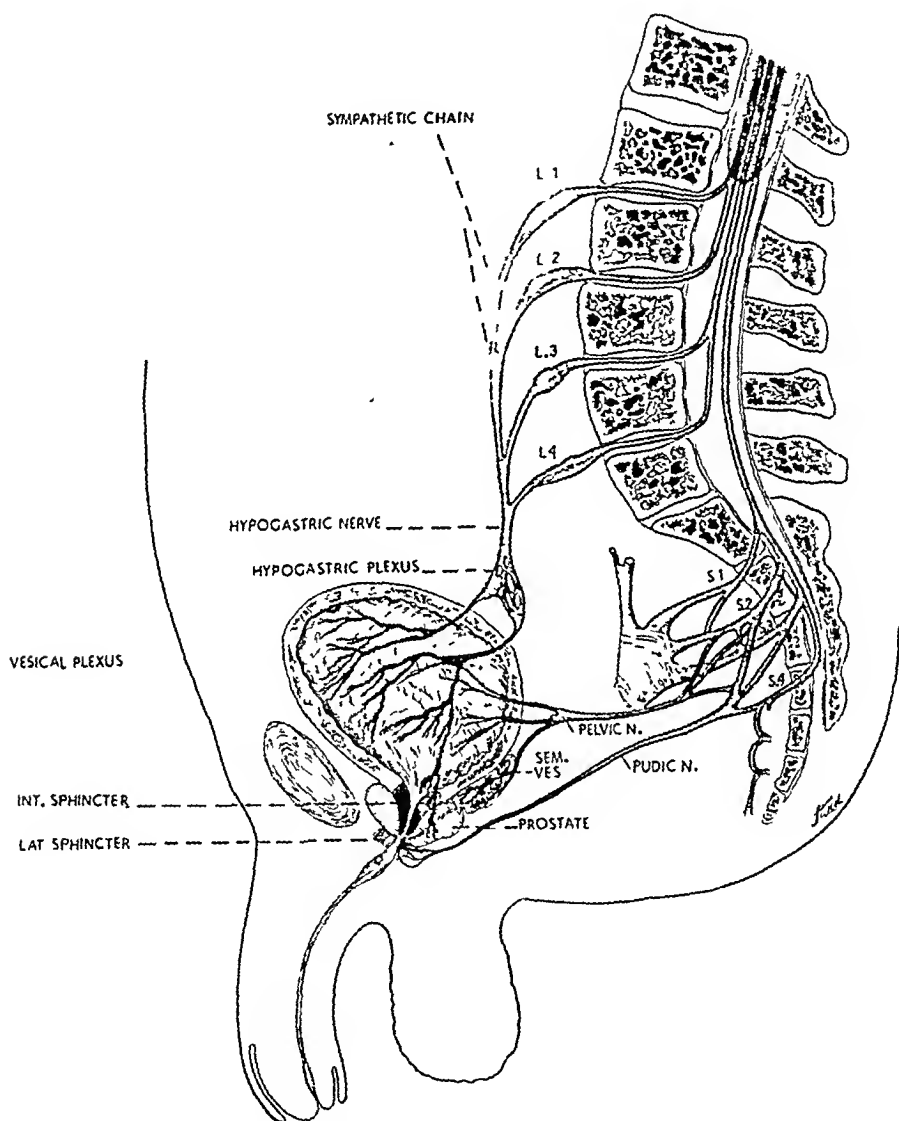


FIG. 3.—Schematic sketch of the nerve supply to the bladder.

1. *Direct violence to the bladder.*—In any procedure in which mobilization of the distal colon is performed, there is bound to be a certain amount of “tearing” of the posterior wall and base of the bladder with resultant edema, which of itself would undoubtedly inhibit normal bladder activity. In the female, obviously, because of the interposition of uterus, broad ligament, tubes, ovaries and vagina, the bladder is less likely to suffer such trauma and the

resultant incidence of bladder dysfunction for this reason alone would be much lower than in the male. All in all, however, trauma to the bladder does not play a major role in postoperative vesical dysfunction.

2. *Nerve injury*.—Postoperative bladder atony is generally ascribed to severance of the autonomic nerves during the operation dissection. The nerve supply to the bladder consists of the presacral nerves (sympathetic fibers arising from spinal cord segments Lumbar 2, 3, 4, 5) and the pelvic nerves

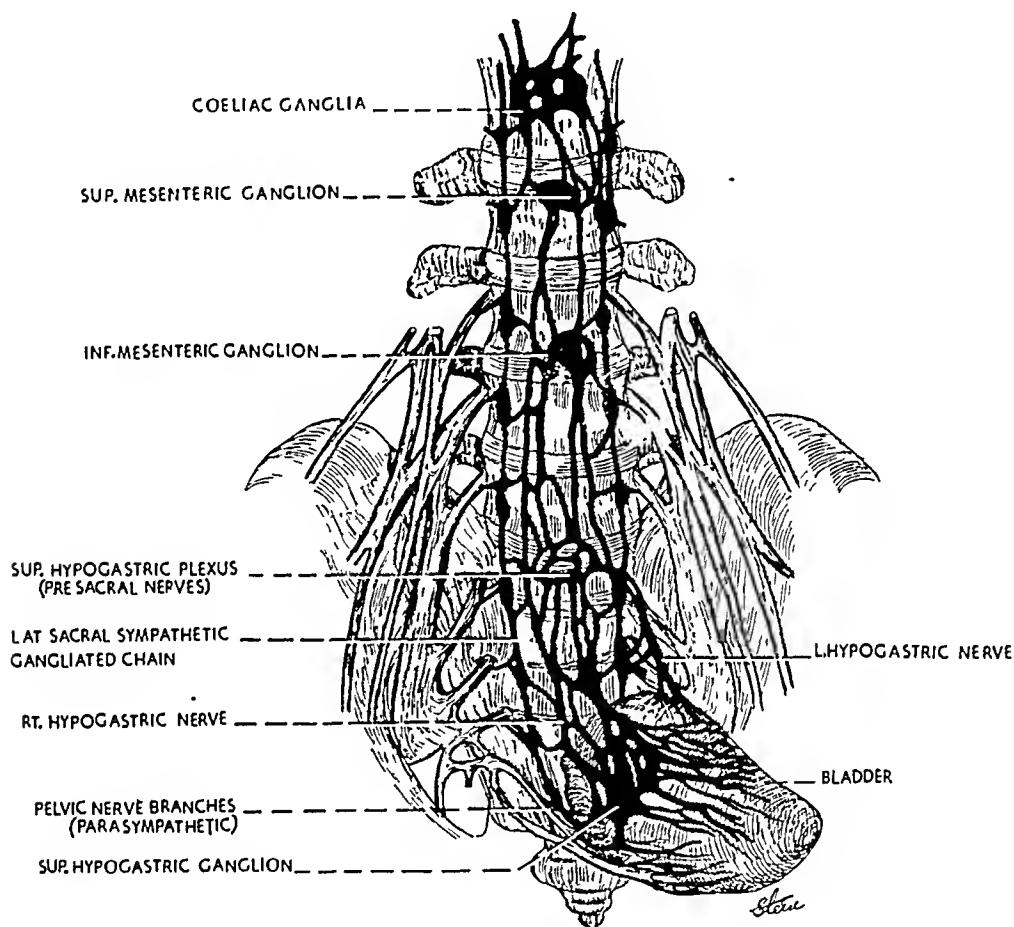


FIG. 4.—Representation of the anatomic distribution of the autonomic nerve supply to the bladder.

(parasympathetic fibers from spinal cord segments Sacral 2, 3, 4); these unite to form the hypogastric plexuses which lie on the pelvic floor, one on each side of the rectum. The sympathetic nerves are less important regarding bladder action than are the parasympathetic fibers, the latter having the function of stimulating the bladder musculature to contract (Fig. 3 and 4). Where injury to these nerves occurs, the bladder becomes unable to contract forcefully, becomes progressively atonic, thus inviting infection. In such cases, postoperative cystometric readings show a flattened curve of intravesical pressure with the patient's first desire to void present only after the bladder is filled with very large amounts of fluid.



Dissection of the rectum with great attention to staying close to the rectal wall would perhaps obviate damage to the autonomic plexuses. In this regard, it is interesting to note that Bacon<sup>1</sup> reports low incidence of vesical dysfunction following proctosigmoidectomy; his technic preserves the anal sphincter musculature and, consequently, there is no extensive perineal dissection and formation of a large posterior wound as in the typical Miles abdominoperineal resection. This undoubtedly lessens nerve trauma and thus postoperative bladder function is less likely to suffer.

3. *Posterior sagging of the bladder*—is said by Marshall et al<sup>7</sup> to play a significant part in the patient's difficulty to void postoperatively. Support to the bladder and prostate in the form of the rectum and sigmoid is absent after the colon resection; consequently, the bladder and vesical neck sag backward, thus producing dysuria. This would certainly help to explain why vesical dysfunction is less frequent in the female, inasmuch as support to the bladder would still be given by the broad ligament, tubes and uterus even after removal of the rectosigmoid.

4. *Vesical neck obstruction*.—As we see it, the obstruction to urinary outflow in the form of prostatic intrusion or median bar is the most important determinant in the problem of bladder dysfunction following colon surgery. Even where the patient prior to operation gives no history of difficulty in voiding, the status postoperatively may be completely changed: we now have a bladder musculature which has been weakened by trauma to the nerves supplying it, competing with an obstructive lesion at the neck of the bladder. Whereas preoperatively, the bladder was "compensated" in its ability to force urine out over a relatively unimportant obstruction at the vesical neck, postoperatively, the bladder becomes "decompensated" and is unable any longer to overcome the same obstructive factor. Anatomically, the amount of tissue which acts as an obstruction may be minute, as it was in one case requiring transurethral resection of the vesical neck where 1.6 Gm. of tissue was resected, or on the other hand, true prostatic enlargement may be present as it was in another case where 80 Gm. of tissue had to be removed in order to establish an adequate waterway. The following case will illustrate the characteristic sequence of events where vesical neck obstruction is present:

**Case 3.** PGH No. K-13322. A retired printer, 72 years of age, who gave a history of slight prostatic obstructive symptoms of several years' duration was operated upon for adenocarcinoma of the rectum; abdominoperineal resection was performed. After removal of the routinely used inlying urethral catheter on the fourth postoperative day, the patient was unable to void. During the subsequent week, though he was able to void with some difficulty, a large residual urine remained in the bladder and urologic consultation was requested 15 days after operation. Cystoscopy was performed with findings of a median bar plus very slight intrusion of both lateral lobes of the prostate. Transurethral resection was performed, with removal of six Gm. of prostatic tissue. Two days after the resection, on removal of the catheter, the patient was able to void with a good stream and completely empty the bladder. There have been no subsequent urinary symptoms and examination shows no residual urine.

MANAGEMENT OF POSTOPERATIVE VESICAL DYSFUNCTION

As is true of almost every problem, prevention would obviate a great deal of distress and in this situation of vesical dysfunction one can, to a great extent, spare the patient much postoperative difficulty. First of all, though the rectal symptoms may be so pronounced as to overshadow every other complaint of the patient, it must be the object of the physician to specifically inquire concerning urinary tract symptoms and to ferret out the presence of any bladder problems. Where a history of urinary difficulty is present, urologic survey and cystoscopy should be done preoperatively. In the presence of obstruction of the vesical neck, transurethral resection should be performed *prior* to colon surgery.

Even in the absence of symptoms suggesting bladder neck obstruction, it might nevertheless be wise to pursue the policy of preoperative cystoscopy, particularly in those male patients where rectal examination shows the prostate to be larger than normal. In many of these patients, cystoscopy will reveal obstruction which should be removed by endoscopic means before the colon lesion is attacked surgically.

Postoperative management commences in the operating room with the insertion of a soft rubber catheter of the self-retaining type. This should be small in calibre, either No. 16 F. or No. 18 F. Because any catheter which is permitted to remain inlying for longer than 24 hours inevitably and invariably leads to urinary infection and because over 90% of these infections are due to coliform organisms, a sulfonamide should be given prophylactically. (We prefer to give either sulfathiazole or sulfadiazine Gm 0.5 every 4 hours with equal amounts of sodium bicarbonate. Sulfathalidine should be administered both pre- and postoperatively.) Bladder lavage with any suitable solution should be done at least three times daily.

In order to overcome the effect of operative trauma to the autonomic nerves supplying the bladder, administration of a parasympathetic stimulant drug is wise; we have found the most effective to be mecholyl bromide in dosages of 200 mg. t.i.d.

After approximately five days of the above regimen, the urethral catheter should be removed. Subsequently, *although the patient may be able to void spontaneously*, he should be catheterized at the end of an eight hour period and the amount of residual urine determined. If this amount is greater than 100 cc., the catheter should be reinserted for several more days, and the residual urine determined again at the end of that period of time. Where a large residual urine and difficulty in urination persist, cystoscopic examination should be performed; further therapy, including the possibility of transurethral resection, will depend upon cystoscopic findings.

Attention to the program outlined above, we believe, will be of considerable help in obviating much vesical discomfort to the patient following his colon surgery.

## SUMMARY

Urologic complications of surgery of the descending colon, particularly in abdominoperineal resection are more frequent than is commonly acknowledged, with 15% of the cases in our series sufficiently serious to warrant management by the urologist.

The majority of these urinary tract complications occur in males, and include injury to the ureter with resultant ureteral fistula, trauma to the bladder causing vesical urinary fistula, and vesical dysfunction. The latter is the most frequent of these urinary tract complications. The necessity for immediate and complete urologic investigation is emphasized when urinary drainage appears in the wound, to the end that renal function may be spared in cases of ureteral fistula.

The most important factors productive of postoperative bladder disability are trauma to the pelvic autonomic nerve plexuses supplying the bladder, and obstruction at the vesical neck. A program of management in the prevention of vesical dysfunction is presented, including preoperative cystoscopy where indicated and transurethral resection of the vesical neck obstruction where such is found either pre- or postoperatively.

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# SACROCOCCYGEAL TERATOMATA IN INFANCY

## A REPORT OF SIX CASES \*

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TERATOMAS AND TUMORS containing structures of trigeminal origin, duplicating with varying degrees of development almost any tissue or organ in the body. They tend to occur along the long axis of the body, especially at its poles. Teratomas of the sacrococcygeal region are relatively uncommon: less than 100 have been reported in the literature.

In the past 30 years at the Children's Memorial Hospital, seven such tumors have been observed. One of these cases, containing a well formed scapula, was reported by Dr. A. H. Montgomery in 1922.<sup>1</sup> The remaining six cases are now presented.

### CASE REPORTS

**Case 1—History.** J. S., a white girl, 11 months of age, was admitted to the Children's Memorial Hospital January 5, 1935. At birth a soft tumor was noted at the base of the spine extending into the buttocks, on the right more than on the left. This mass had never been tender or inflamed but gradually doubled in size. There was no weakness or loss of sensation in the lower extremities.

**Examination.** Physical examination was essentially negative except for the tumor mass over the lower sacral region extending into the buttocks. It was soft, irregular in contour, and about the size of a grapefruit. The skin over it was tense with bluish discoloration in the midline. The lower extremities were normal. The blood count and urinalysis were normal. Roentgen-ray examination revealed no abnormality in the spine and no bone was seen in the tumor mass.

**Operation.** Under ether anesthesia a transverse incision was made across the tumor, exposing an encapsulated mass. This was dissected free and removed. The defect in the pelvic floor was repaired by suture of the levator ani muscles and the wound closed in layers without drainage. A transfusion of 250 cc. of whole blood was given immediately following surgery. The wound healed well and the patient was discharged on the twenty-first postoperative day.

**Pathologic Report.** The specimen consisted of an encapsulated oval mass, weighing 280 Gms. On the surface was a coiled piece of intestine 20 cm. long with its own mesentery. It contained material having the gross appearance of meconium. The central portion consisted of fat fibrous tissue and small areas of cartilage. One section suggested corpus luteum or adrenal cortical tissue.

Microscopic sections revealed fatty and fibrous tissue with scattered structures resembling adrenal glands, fallopian tube, gastric mucosa, renal pelvis and a fully developed portion of small bowel wall.

A diagnosis of nonmalignant teratoma was made.

**Course.** One year after surgery a mass was noticed in the right buttock at the operative site. This gradually increased in size. Four roentgen-ray treatments were given. On March 13, 1936, the patient was readmitted to the hospital. Examination revealed only the mass described above. The following day the scar and an orange-sized cystic mass were removed. It was rather firmly adherent to the rectum. Another transfusion had to be given.

\* Submitted for publication, September 1947.

*Pathologic Report.* The specimen was a firm, 5x6.5 cm., poorly encapsulated mass, containing cysts, firm fibromyxomatous tissue and areas of pink, softer tissue. One area was soft and bright yellow and another contained cartilage.

The microscopic sections showed columnar cells with a tendency to acinar formation, proliferating fibroblasts, smooth muscle and embryonal fat. The diagnosis was recurrent teratoma with malignant changes.

On June 20, 1936, the tumor had recurred in the same area and was removed again. The patient's family cannot be contacted to discover the outcome of this case but it is presumed that she died of recurrence.

**Case 2.—History.** C. Z., an 11-day-old white female was admitted March 4, 1937. At delivery a mass had been noticed in the region of the left hip and back. It had slightly increased in size. The bowels moved frequently and on two occasions blood was passed.



FIG. 1.—Case 2, on admission to hospital.

*Examination.* There was a large cystic mass in the sacroccygeal area, pushing the rectum forward and displacing the anus to the left. (Fig. 1.) The cyst transilluminated and seemed to contain a ballotable mass. Roentgen-ray examination revealed areas of increased density in the mass but no spina bifida. (Fig. 2.) To rule out meningocele, 30 cc. of turbid strawcolored fluid were aspirated from the tumor. There was no sinking of the fontanelle but following aspiration hard masses could be felt in the tumor.

*Operation.* On March 12, 1937, a skin incision was made along the upper border of the mass and the skin flap reflected downwards. The cyst contained yellow fluid and two small hard masses. It was dissected free from its attachment in the region of the sacrum behind the rectum. Tissue in this region was white, hard and gristle-like. The wound was closed in layers and drained.

*Pathologic Report.* The specimen consisted of a cyst wall and two hard masses of tissue.

Microscopic sections revealed brain tissue, cartilage, bone, fatty areolar tissue, fibrous reticulum and sebaceous glands. One section resembled the floor of the lateral ventricle of the brain. Another revealed epithelial structures simulating renal pelvis and tubules.

*Course.* The wound healed and the child was discharged on the thirty-first post-operative day. Roentgen-ray therapy was given.

On December 16, 1937, the child was readmitted for constipation followed by diarrhea, abdominal distention and vomiting of two days' duration. Examination revealed the bladder above the umbilicus. In addition, rectal examination revealed a large, soft, non-tender mass lying in the hollow of the sacrum, pushing the rectum forward. There was a small mass above the operative scar in the sacral region.



FIG 2—X-ray of same patient (Case 2) showing areas of calcification in the soft tissue mass.

Bladder drainage was instituted. Cystograms and intravenous pyelograms revealed a large bladder with some hydro-ureter and clubbing of the minor calyces. The urine contained pus, staphylococcus aureus and *E. coli*. An abscess on the buttock drained spontaneously after the patient had run a febrile course for two months. Three months later another abscess formed on the back and was drained. The urinary condition had markedly improved. A mild secondary anemia developed. Another course of roentgen-ray therapy was given. Sinuses about the sacral region continued to drain.

The child died at home in 1942, presumably because of the tumor.



FIG. 3.—Cross section of tumor removed from Case 3, showing the typical cystic nature.

**Case 3—History.** P. T., a white girl, age eight months, entered the Children's Memorial Hospital on October 2, 1942, with the history of having had a lobulated, cystic growth in the left buttock since birth. This mass had grown larger and become more superficial, extending into the right buttock. Aside from frequency in stools since birth, the history was otherwise negative.

**Examination.** The examination revealed a multilocular, cystic tumor mass covered with tense skin occupying the left buttock and medial one-third of the right buttock posterior to the rectum. A hemangioma of the left calf was present. The hemoglobin was eight grams; red blood cell count was 3,600,000; white blood cell count was 16,300. The urine was negative.

*Operation.* The day following admission a large multilocular cyst was removed from the sacrococcygeal region. The child was given 110 cc. of whole blood in the operating room. The wound healed well and the child was discharged the seventh postoperative day.

*Pathologic Report.* The specimen consisted of an irregular lobulated mass 11 x 9.5 x 4 cm. and weighed 280 Gm. Some portions were cystic; other portions were solid. The capsule was 2 mm. thick. The largest cyst was 4.5 x 4 x 2 cm. and contained thin, yellow fluid. The microscopic sections revealed smooth muscle, cartilage, bone, adipose tissue, squamous epithelium and nervous tissue. One section revealed glandular tissue with papillary features. The epithelium was pleomorphic with irregular nuclei and disorderly atypical mitosis.

A diagnosis of teratoma with an area of embryonal carcinoma was made (Fig. 3.)

*Course.* On January 10, 1943, the patient was readmitted with the history of recurrence of the tumor above the healed incision three weeks previously. This mass had increased in size and the patient had lost four pounds of weight. Examination revealed a firm, fixed bluish lump the size of a walnut above the incision over the sacrum. This was resected and the wound healed well.

*Pathologic Report.* The specimens consisted of two yellowish gray pieces of tissue  $1\frac{1}{2} \times 1\frac{1}{2} \times 1\frac{1}{2}$ ". The microscopic section revealed cartilage, adipose and fibrous tissue and glandular tissue with less mitosis than the tumor showed previously.

No trace of this patient can be found. It is probable that she also died of recurrence of the tumor.

**Case 4—History.** J. C. was a full term white baby girl. One week after a normal delivery a small tumor had been felt in the left buttock. It grew rapidly in size and at the age of two weeks the child developed urinary retention and was taken to another hospital. Catheterization did not relieve the abdominal distention, so a laparotomy was performed. It was reported that rupture of the bladder and peritonitis were found. The bladder was repaired and drained through a urethral catheter. A small biopsy was taken from a large mass lying in the pelvis behind the bladder. Microscopic sections revealed "nerve tissue having the appearance of brain tissue." Two weeks later the mass in the buttock was removed. The child made a fairly good recovery and at the age of two months was admitted to the Children's Memorial Hospital on May 12, 1941.

*Examination.* The infant was poorly nourished. Her abdomen was distended. A hard mass could be palpated rising out of the pelvis and lying posterior to the rectum. A small, indurated, healed wound was present on the left buttock under which could be felt a large firm mass, extending into the hollow of the sacrum. There was an indwelling urethral catheter. Intravenous pyclograms disclosed an enlarged bladder and hydro-ureters. The hemoglobin was 85 per cent; the red blood cell count was 4,300,000; the urine contained four plus albumin, numerous white blood cells and an occasional red blood cell.

*Course.* Roentgen-ray therapy was given but produced no decrease in the tumor size.

Microscopic examination of a biopsy of the mass in the right buttock revealed dense fibrous tissue containing cystic spaces lined with squamous, low cuboidal and tall columnar epithelium. In some areas there were papillary projections. There was evidence of reaction to irradiation, the bladder function returned to normal and the child was discharged in good condition, although the tumor on the buttock was gradually increasing in size.

On September 12, 1941, the child was readmitted with the acute intestinal obstruction and died 24 hours later.

*Postmortem Findings.* The examination was limited to the reopening of the surgical incisions. There was a large, multiloculated, cystic tumor rising retroperitoneally in the abdomen, 2 cm. above the umbilical level and extending down between the rectum and



sacrum into the buttock. It was attached by firm fibrous adhesions to the coccyx. Cut sections revealed cystic cavities varying markedly in size and in the thickness of their walls. Scattered among the cysts were several white, granular, homogenous nodules and areas of soft, pinkish gray tissue. In addition there was bilateral hydronephrosis, hydro-ureter and ascites.

Microscopic sections showed cystic spaces lined with epithelium similar to those found on biopsy. Some areas resembled gastric mucosa and one section appeared to be pancreatic

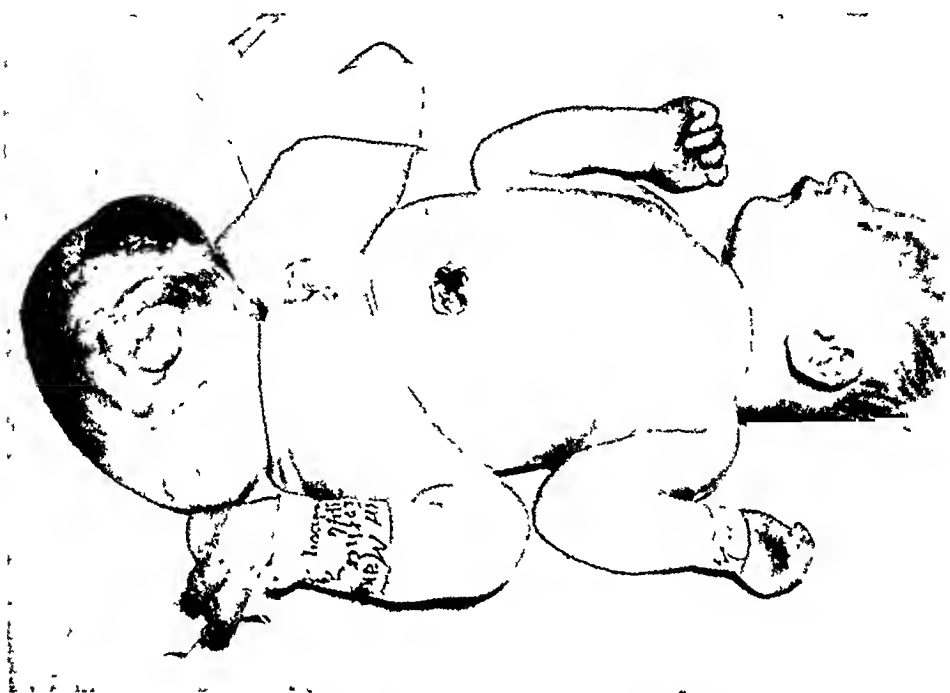


FIG. 4.—Case 5, on admission to hospital.

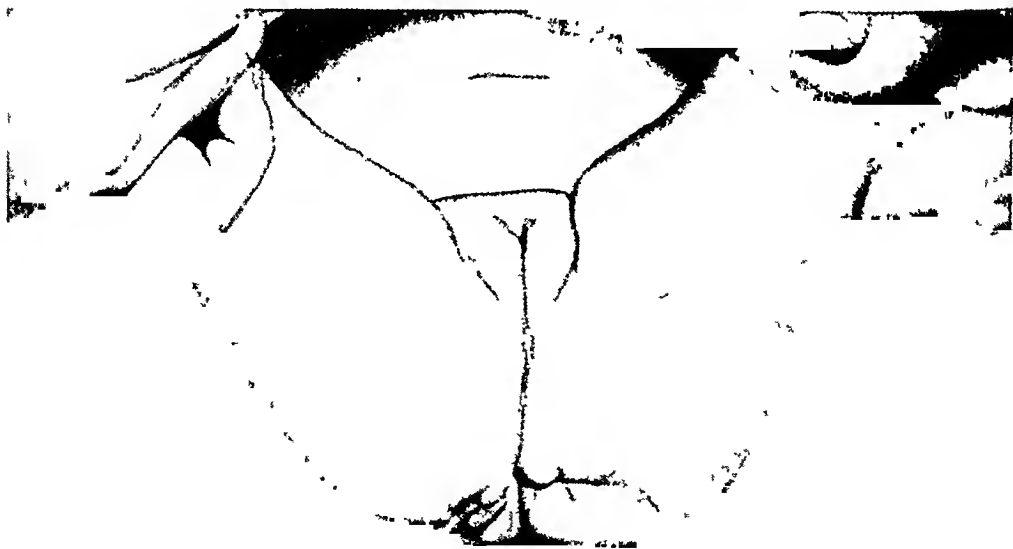


FIG. 5.—Case 5, three months postoperatively.

tissue. There were large aggregates of atypical ganglion cells and nerve fibers in collagenous connective tissue. Peri-aortic nodes showed no metastasis. A diagnosis of teratoma without evidence of malignant changes was made.

**Case 5—History.** M. was a white female, one day old, weighing seven pounds, two ounces, admitted to the Children's Memorial Hospital on June 1, 1946. At birth a large tumor attached over the sacrum was noted (Fig. 4).

**Examination.** The infant was normal except for a large, irregular tumor lying over the lower sacral region. It was covered with skin except for a small ulcerated area. Urinalysis and blood count were normal. Roentgen-ray examination revealed no bony pathology in the spine but the tumor mass 8 x 12 cm. could be visualized containing areas of calcification. The diagnosis of sacrococcygeal teratoma was made.



FIG. 6.—Cross section of tumor removed from Case 5.

**Operation.** The tumor was removed the same day. A circular incision was made about the base and the mass dissected free. It extended behind the rectum into the hollow of the sacrum. Considerable bleeding was encountered and the infant went into shock. Rapid transfusion of 250 cc. of whole blood revived the patient and the closure of the wound was completed.

**Pathologic Report.** The tumor measured 12 x 10 x 5 cm. and weighed 320 Gm. It contained cysts and calcified areas at the base. Near the skin surface were dark red lobulated masses and firm round nodules (Fig. 6).

Microscopic sections revealed glial tissue and some areas resembling choroid plexus, fatty tissue with nodules of cornified squamous epithelium and sweat glands with bodies having the appearance of hair. Fibrous tissue contained cells varying in size, shape and staining reaction with some mitosis and occasional giant cells. Other sections revealed cartilage, smooth and striated muscle and pseudostratified columnar ciliated epithelium. A diagnosis of teratoma was made.

**Course.** Recovery was uneventful and the wound healed well. The patient was discharged on the eighteenth postoperative day. At the present time the patient is healthy

and shows no recurrence of the tumor (Fig. 5).

**Case 6—History.** J. T., a 3½ month old white female was admitted to the hospital October 26, 1944, for constipation due to a congenital anal stricture and a hard mass in the right buttock present for three days.

**Examination.** There was an anal stricture and a rectovaginal fistula. The right buttock was swollen, hard and tender and one week later pus drained spontaneously from the intergluteal fold. Two months later the abscess reformed and was incised.

**Course.** A draining sinus remained in the sacrococcygeal area. Frequent rectal dilations were necessary. On July 26, 1945, a colostomy was performed. A year later the child was readmitted.

**Operation.** On July 31, 1946, an incision was made in the sacral region and a cystic structure was found imbedded in dense scar tissue. This extended down toward the sacrum and was dissected free. Attached to it was a second, smaller cyst which was likewise removed. Some clear fluid escaped which resembled spinal fluid. The wound was closed in layers without drainage.

**Pathologic Report.** The specimen consisted of a dumbbell-shaped piece of tissue 5 x 2 cm. containing a cyst with a smooth lining and filled with milky fluid. Microscopically the cyst was lined with stratified squamous epithelium surrounded by dense fibrous tissue. Other areas showed columnar epithelium, loose myxomatous connective tissue and nerves. One area contained ganglion cells imbedded in a fibrillar network resembling neurological tissue. A diagnosis of a benign teratoid tumor was made. Because no structures of entodermal origin could be found, the tumor more closely resembled a dermoid cyst.

**Course.** The wound healed well and there has been no recurrence to date. The rectovaginal fistula is to be repaired soon.

#### DISCUSSION

**Incidence.**—Calbet<sup>2</sup> stated that congenital tumors of the sacrococcygeal regions occur once in 34,582 births. Teratomas represent only a very small percentage of these tumors.

The tumors are thought to be invariably present at birth and about 90 per cent of them are recognized at that time. Very few remain unnoticed until adult life. A large percentage of the patients are stillborn or die shortly after birth. Because of their size, these tumors may cause dystocia.<sup>3</sup>

Chaffin<sup>4</sup> reports that 75 per cent of the patients with these tumors are females. In our series all six of the cases were female.

In the past 30 years there have been a little over 600 tumors examined pathologically at the Children's Memorial Hospital. Seven of these were sacrococcygeal teratomas, giving an incidence of approximately one per cent of all tumors in this hospital.

**Origin.**—The origin of these tumors is the only really controversial aspect of teratology. Two main theories have been advanced.

1. Parthenogenic development of the individual's primitive germ cells might give rise to these tumors as is suggested by the experimental work of Bosarus<sup>5</sup> with stimulation of unfertilized frog ova. These germ cells migrating from the primitive streak of the genital ridge could lodge in the sacrococcygeal region. Similarly, in early embryonic life a blastomere resulting from segmentation might begin its own development remaining attached to the main embryo and becoming incorporated in it. If the former occurred, the teratoma

would represent an offspring while in the latter case it would be a twin. It is easy to believe that sacrococcygeal teratoma are rudimentary organ masses representing an ill-developed pygopagus twin.

2. Other authorities believe that these tumors are not fetal implants but arise primarily from cells already present in the sacrococcygeal region in normal embryonic development such as the postanal gut and the neurenteric canal. The close approximation of nervous, intestinal, bony and connective tissue elements in this region is supposed to explain the development of tumors containing structures from all three germ layers.<sup>2</sup>

Chaffin suggests that temporary adhesions between the fetal rump and the amnion may cause formation of teratomas.

*Pathology.*—Teratomas are usually lobulated tissue masses with cystic and solid areas and may contain tissue or malformed organs representing any structure in the body. The most common contents are epithelial lined cysts, connective tissue, ganglion cells and other nervous elements, intestinal mucosa, bone and cartilage. Infrequent tissues are liver, pancreas, kidney, testicle, ovary and chorionic epithelium. Malignant changes will be discussed below.

*Clinical Features.*—Teratomas of this region always have their origin retrorectally and are attached to the coccyx or sacrum.<sup>6</sup> From there they usually grow downward and posteriorly into the buttocks, displacing the anus forward and to one side. They may also extend upward behind the rectum into the abdominal cavity.

The tumors vary in size from a scarcely noticeable lump to a huge mass interfering with bodily function. They are covered with skin but often have ulcerations or fistulae. They may be cystic or solid but usually contain areas of both. Bone may be felt within the tumors and occasionally peristalsis can be observed. Upon stimulation, muscular twitching may be present.

Aside from local examination, it is important to examine the abdomen for evidence of extension of the mass producing urinary or bowel obstruction. Rectal examination will reveal the extent of pelvic growth and the degree of fixation to the rectum. Roentgen-ray is helpful in showing the presence of bone or teeth and in determining spinal development. Aspiration of cystic areas in the tumor is of doubtful help and often leads to infection and fistula formation. Other congenital anomalies are frequently present.

*Differential Diagnosis.*—Other causes of a mass in the sacral region may be meningocele, hernia, abscess, chordoma, dermoid, lipoma, myoma, angioma, myeloma, sarcoma, tuberculosis of sacrum or rectal carcinoma. The last few would be extremely rare in infants.

An accurate diagnosis is necessary in order to determine the proper treatment.

DeVeer and Browder<sup>7</sup> have emphasized several points to differentiate a teratoma from a meningocele. The latter is smaller and does not increase in proportion to the infant growth as does a teratoma. A meningocele is covered by a translucent membrane whereas a teratoma is covered with skin. The

rectum is not often displaced by a meningocele but it is by a teratoma. There is usually evidence of communication between a meningocele and the spinal canal such as expansion of the tumor with coughing and crying or bulging of the fontanelle upon compression of the tumor. Neurologic signs in the lower extremities are more often associated with a meningocele. A roentgenogram of the spine showing spina bifida, also suggests meningocele.

The possibility of the tumor being a rare type of hernia may necessitate a barium meal study to demonstrate continuity of the bowel in the abdomen and in the tumor.

*Complications.*—1. Malignancy—Sacroccygeal teratomas develop malignant changes in about 15 per cent of the cases. In 1942 Lisco<sup>8</sup> collected 12 cases of malignancy from the 72 teratomas reported up to that time. In our own series, cases I and III contained definite malignant elements and developed local recurrences of the tumors.

Usually only one tissue of the teratoma becomes malignant. This resembles a sarcoma as to the method of spread and tendency to local recurrence.<sup>9</sup> Pathologically, however, the malignant areas usually are either papillary carcinomas or neoplasms of neural origin.

Rapid growth of a teratoma does not necessarily indicate malignancy because growth of the tumor usually parallels that of the child. The presence of well-formed bony structures, muscular twitching or bowel with peristaltic activity indicates a benign tumor.<sup>10</sup>

2. Ulceration, infection and fistula formation may develop as occurred in case II and case VI.

3. Obstruction of the rectum or lower urinary tract may occur if the tumor expands in the hollow of the sacrum. This has been noted frequently in medical literature<sup>11, 12, 13</sup> and occurred in case II and IV.

4. Very rarely hypersecretion of some endocrine gland in the teratoma may produce generalized effects. Rhoden<sup>13</sup> reported a case of precocious sexual development which he thought was due to the secretion of the adrenal cortical tissue in the teratoma.

5. The position and large size of some teratomas may become a nuisance and discomfort. A case reported by Brines<sup>14</sup> had a very large tumor containing rudimentary arm and hand bones that made sitting or walking quite difficult.

*Treatment.*—It is agreed that complete excision of the tumor as early as possible is the treatment of choice. More and more cases of successful removal of teratomas have been reported in the past few years. Operation in the first year of life gives better results as to recurrences and mortality than if surgery is postponed until later life.<sup>4</sup> Postoperative radiation therapy may also be given especially if pathological examination reveals malignant elements.

Pearse<sup>9</sup> emphasizes that the posterior approach is the best because: 1) complete removal of the tumor with resection of the coccyx, if necessary, is more easily accomplished; 2) the peritoneal cavity is avoided; 3) hemorrhage is

controlled more readily; 4) local recurrences in the scar are easily seen and treated. All the cases operated upon at this hospital have been approached posteriorly.

It is interesting to note the degree of shock that usually accompanies the removal of these tumors. Some authors mention that shock seemed out of proportion to the blood loss.<sup>10, 12, 15</sup> The reasons for this may be several. A large vascular bed is being removed. The region from which the tumor is removed is normally quite vascular and hemostasis is difficult. Also, the degree of blood loss in infants is deceptive. A few blood-dampened sponges may represent a large fraction of the baby's blood volume.

It will be noted that in several of our cases a transfusion was necessary during or immediately after the operation. In case V the infant would have succumbed were it not for rapid replacement of blood loss. In this case a transfusion of 250 cc. of blood was given. Considering the weight of the patient, this represents almost a complete replacement of the total blood volume of the infant.

It has been our practice in all such major procedures to insert a cannula into the long saphenous vein at the ankle and attach to it intravenous tubing and a three-way stopcock to which is connected a 50 cc. syringe and a Salvarsan flask with a Murphy drip tube. During the operation physiologic saline solution is allowed to drip slowly to keep the system open. If necessary, citrated whole blood can be poured into the flask and pumped into the patients' vein quite rapidly by means of the syringe.

#### SUMMARY

1. Six previously unreported cases of sacrococcygeal teratomas are presented. All of these were females below the age of one year. Removal of the tumor was attempted in five cases. Malignancy and recurrence occurred in two cases and probably a third. One child died as the result of pressure of the tumor causing urinary and bowel obstruction. Two cases are living and well one year after surgery with no evidence of recurrence.

2. Some clinical aspects of these tumors are reviewed with emphasis on treatment by early and complete surgical excision via the posterior route.

3. A well-known but not widely used method of giving a rapid, often life-saving, transfusion during operation is described. In the removal of these tumors as well as many other major operations on infants the survival of the child may depend on the ability to replace rapidly a serious blood loss.

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# TEMPORARY INTERRUPTION OF THE SYMPATHETIC IMPULSES TO THE HEAD BY INFILTRATION OF THE CERVICAL SYMPATHETIC TRUNK \*

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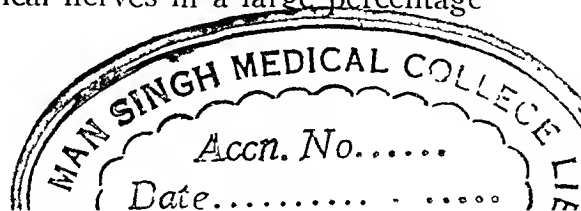
INVESTIGATION OF THE GROSS ANATOMIC relations of the cervical and upper thoracic portions of the sympathetic trunk was undertaken in an attempt to evaluate the various methods of injection for interrupting the sympathetic impulses to the head. Thirty-three cadavers were dissected to determine the typical relations of these parts of the sympathetic nervous system. These observations have been correlated with those made during injections by various methods to block the flow of sympathetic impulses to the head.

Several methods have been described by which the flow of sympathetic impulses from the upper thoracic and lower cervical segments may be interrupted temporarily by injection of various anesthetic agents.<sup>1-6</sup> Most of this work has been stimulated by the need of satisfactory therapeutic measures for vasospastic diseases of the upper extremities. Such transient interruption of sympathetic impulses not only is valuable therapeutically but is of aid in predicting the reaction to surgical interruption of the pathways in question.

Since, in blocking this portion of the sympathetic outflow, the usual goal has been to produce temporarily the conditions present in a sympathectomized extremity, the various methods of injecting the inactivating solutions have been directed toward the cervicothoracic ganglion. This is the most strategic point to attack in order to cut off sympathetic impulses to the upper extremity by such an injection. This ganglion also is a point through which the majority of the sympathetic impulses to the head must pass (Fig. 1), although only a small percentage of such impulses is relayed to ganglionic neurons at this level. Therefore, it is not surprising that, in those diseases which respond favorably to interruption of the sympathetic nerve supply to the head, a technic identical to that employed in blocking sympathetic impulses to the upper extremity generally is used.

A review of the neuro-anatomy involved in the transmission of the impulses is essential for an adequate estimation of the problem. The majority of preganglionic fibers which carry sympathetic impulses to the head issue from the central nervous system via the anterior roots of the lower cervical and upper thoracic spinal nerves (Fig. 1). There is evidence that a few such fibers arise from as low as the fifth or sixth thoracic segment<sup>7</sup> and probably many preganglionic fibers emerge in the lower cervical nerves in a large percentage

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of cases. The latter undoubtedly are of considerable importance in transmitting sympathetic impulses to the head. Most of these fibers destined to transmit impulses to the head ascend the sympathetic trunk to terminate in the superior cervical ganglion. However, some such fibers pass through this ganglion to synapse on scattered small nests of nerve cells located in close relation to the large arteries. The nerve impulses upon reaching the superior cervical ganglion or other peripheral cell station are relayed via postganglionic fibers (Fig. 1) to the effector units, i.e., a smooth or cardiac muscle or gland cells.

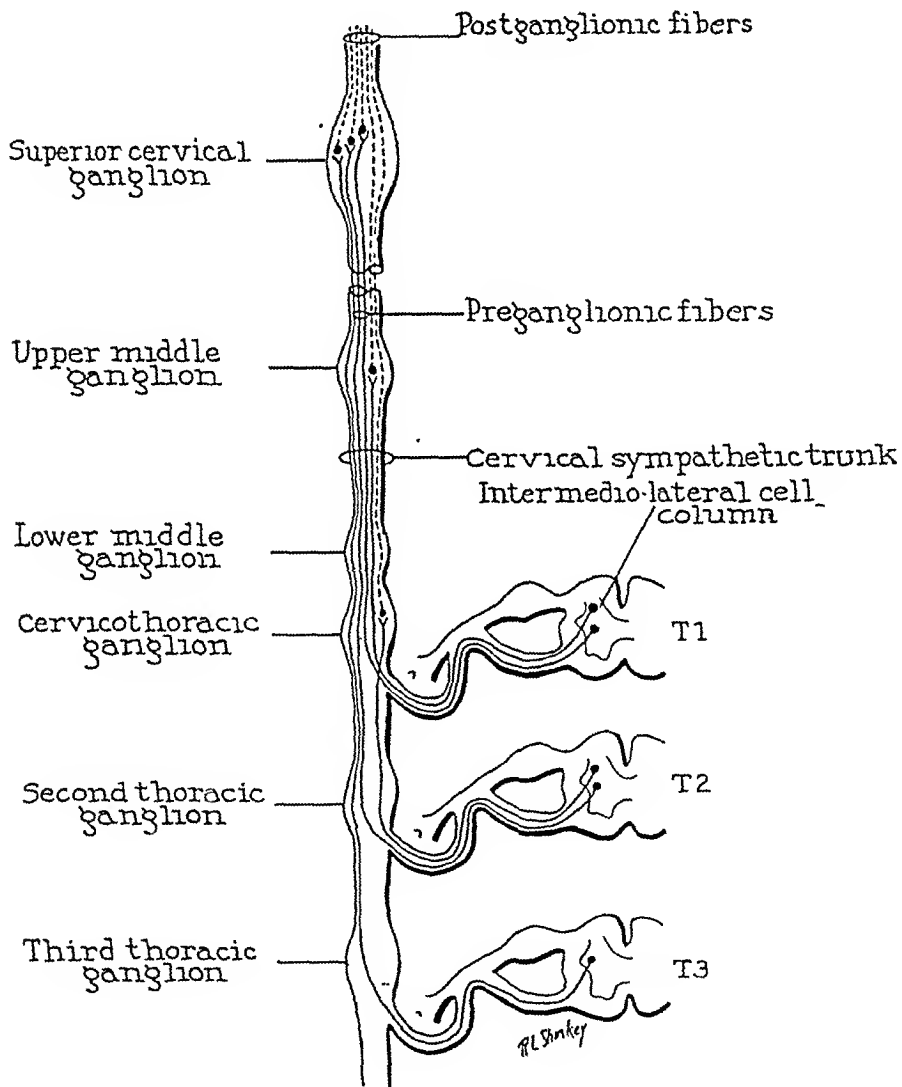


FIG. 1.—Diagram showing synaptic relations of sympathetic fibers to the head.

The postganglionic fibers of the superior cervical ganglion as well as a few postganglionic fibers from more inferiorly located ganglia, a small number of accompanying sensory fibers, and the few preganglionic fibers which pass through the superior cervical ganglion form practically all the fibers of the external and internal carotid plexuses and their subsidiary plexuses. These fibers supply the blood vessels of the face, scalp and most of the brain as well

as the other smooth muscles and many of the gland cells of the head. The majority of the postganglionic sympathetic fibers for the head, which do not arise from cells of the superior cervical ganglion, have their origin in the upper middle cervical ganglion; a smaller number arises in the lower middle cervical ganglion, and still fewer from the cervicothoracic ganglion (Fig. 1).

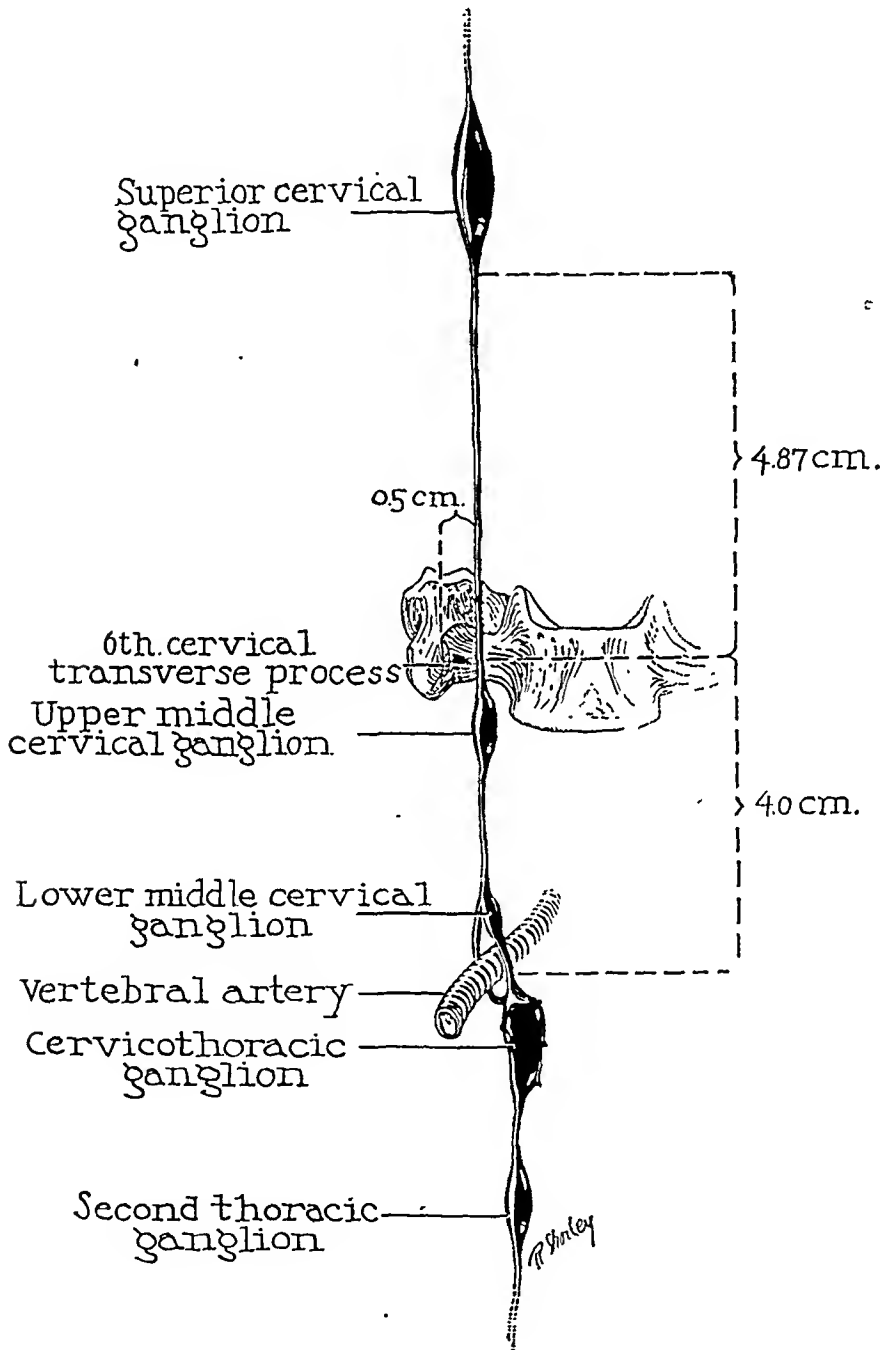


FIG. 2.—Diagram showing average distance of superior cervical and cervicothoracic ganglia from transverse process of sixth cervical vertebrae and average distance of sympathetic trunk from the lateral aspect of the sixth cervical transverse process.

The postganglionic fibers from the upper and lower middle cervical ganglia and the cervicothoracic ganglion with the preganglionic fibers for the middle cervical ganglia and the superior cervical ganglion and a few sensory fibers

form the major part of the cervical portion of the sympathetic trunk. Some postganglionic fibers for the head, as those of the common carotid plexus, extend upward in close relation to the common carotid artery, and a few travel superiorly along the vertebral artery and terminate in its area of distribution. Most of the impulses which travel along the common carotid and vertebral plexuses as well as those which traverse the cervical sympathetic trunk pass through the cervicothoracic ganglion.

Thus, it is obvious that injection of an anesthetic agent about the cervicothoracic ganglion is an effective method of blocking the sympathetic impulses to the head. It interrupts not only most of the impulses which travel via the cervical sympathetic trunk but also many of those passing along the common

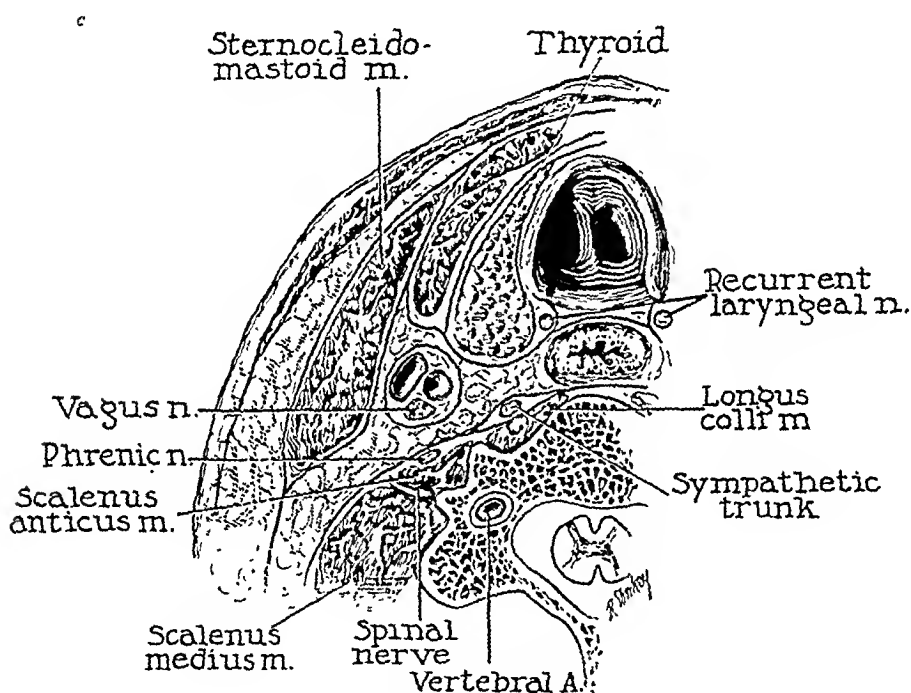


FIG. 3.—Cross section of neck showing relations of sympathetic trunk.

carotid and vertebral plexuses. However, most of the fibers which form the intracranial extension of the carotid and vertebral plexuses undoubtedly join them as segmental branches from the upper part of the cervical portion of the sympathetic trunk.

Although infiltration of the cervicothoracic ganglion is a benign procedure, it seems less so to the patient than injection of the sympathetic trunk at a higher level and actually is accompanied by several potential complications not shared by the latter method. These include, principally, puncture of the apex of the lung, trauma to a portion of the brachial plexus with subsequent pain in the upper extremity, neck, or thorax, and puncture of the large vessels of the lower portion of the neck and upper part of the thoracic regions.

The sympathetic impulses to the head can be efficiently interrupted temporarily by injection of procaine hydrochloride or other suitable anesthetic agent about the cervical portion of the sympathetic trunk. Such an injection can be done relatively painlessly. The greater ease with which the cervical sympathetic trunk can be infiltrated is an advantage. It can also be done with speed and exactness because of certain anatomic relations. It should be noted that the close approximation of the cervicothoracic ganglion to the posteromedial aspect of the vertebral artery and to the subclavian artery almost completely obviates its actually being injected without transfixing one of these vessels with the needle. The various technics described for blocking the impulses which pass through the ganglion actually are methods of infiltration. The chances for occurrence of complications are reduced by introducing

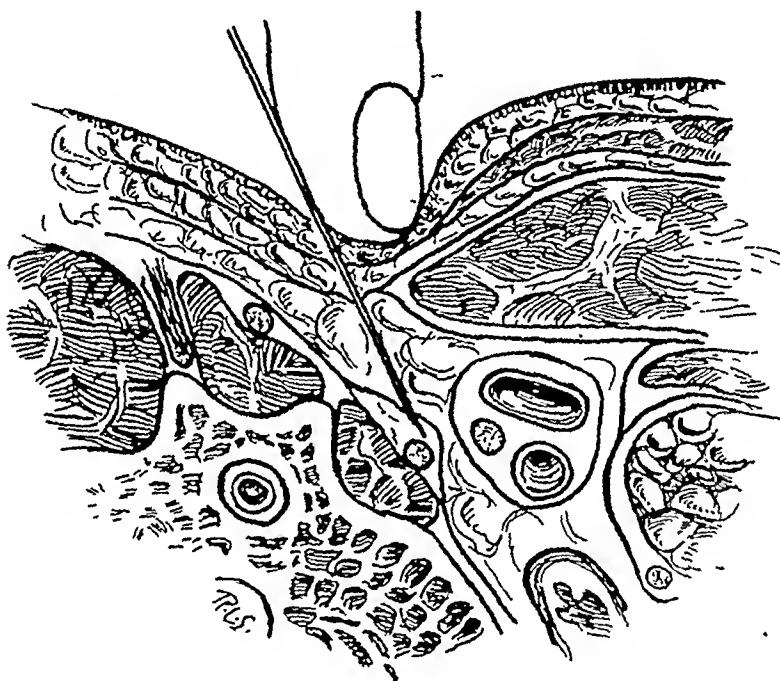


FIG. 4.—Method of palpation of tubercle of transverse process and insertion of needle.

the solution at a comparatively high level as described by de Sousa Pereira<sup>5</sup> and Caldwell and Broderick.<sup>6</sup> However, this also reduces the effectiveness of the block as far as the upper extremity is concerned unless a relatively large amount of the anesthetic agent is used. The average distance of the upper pole of the cervicothoracic ganglion from the middle of the anterior surface of the sixth cervical transverse process in our anatomic studies was found to be 4.0 cm. on the right and 4.2 cm. on the left (Fig. 2). This distance ranged from 2.7 to 4.8 cm. on the right and from 3.0 to 4.9 cm. on the left.

The principal factor in favor of successful inactivation of the cervical sympathetic trunk by injection is the relation of this part of the sympathetic trunk to the carotid tubercle and the anterior tuberosity on the transverse process of the fifth cervical vertebra. Examination of other anatomic relations

in this area demonstrates amply why this technic is uniformly successful. The sympathetic trunk at the level of the fifth and sixth cervical vertebrae lies on the longus colli muscle, medial and slightly anterior to the fibers of the scalenus anticus muscle in a small compartment formed by the splitting of the prevertebral fascia. It is posteromedial to the carotid sheath and its contents (Fig. 3). The latter structures can be palpated easily at this level just deep to the anteromedial margin of the sternocleidomastoid muscle. It is a simple matter to retract the contents of the carotid sheath laterally and palpate the carotid tubercle of the tuberosity on the anterior surface of the transverse

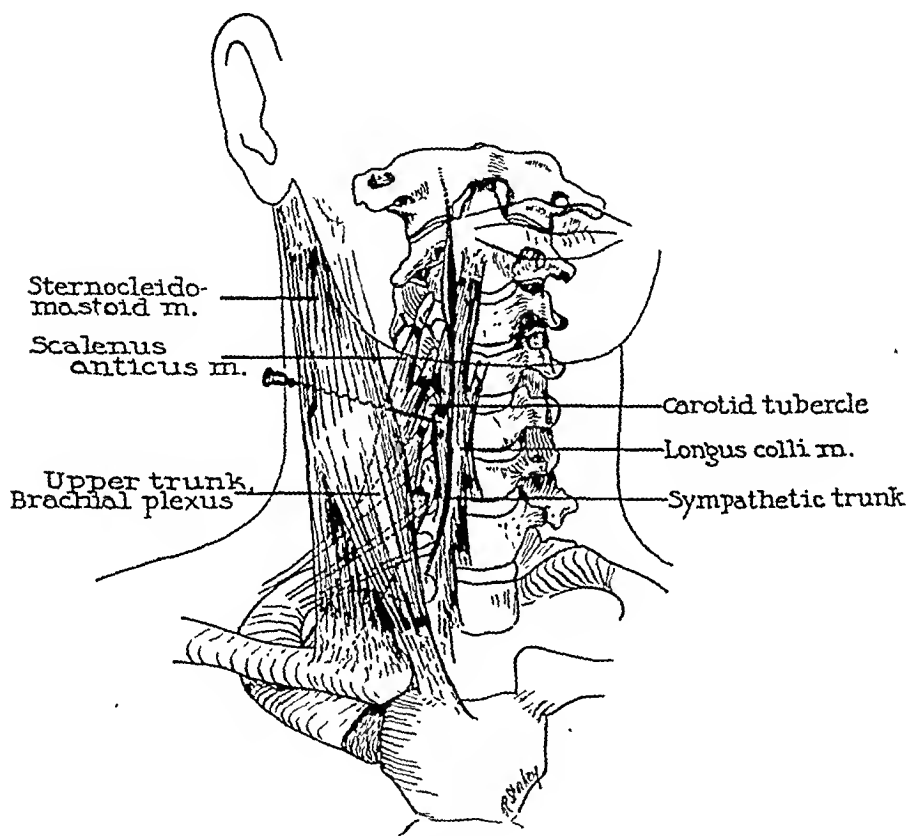


FIG. 5.—Diagram showing relationship of the needle to the sympathetic trunk and adjacent structures.

process of the fifth cervical vertebra. Frequently, it is even easier to palpate these tuberosities by retracting the sternocleidomastoid muscle and the contents of the carotid sheath medially (Fig. 4). It should be stressed that at this level the sympathetic trunk is separated from the vagus nerve by the relatively tough carotid sheath and part of the prevertebral fascia, and from the phrenic nerve by the latter fascia as well as the fascia of the scalenus anticus muscle. The recurrent laryngeal nerve also is well isolated from the sympathetic trunk. When the upper middle cervical ganglion is present, as it has been in approximately 75 per cent of the bodies examined, it lies at or slightly below the sixth cervical transverse process in the majority of instances. It should also be

pointed out that the roots of the brachial plexus and the vertebral artery at this level are safe from injury by a penetrating needle because of their separation from the sympathetic trunk by the transverse process. The inferior thyroid artery is medial to the sympathetic trunk at the level of the sixth cervical transverse process, having crossed behind the trunk at the level of the seventh cervical segment.

In all 66 dissections the sympathetic trunk lay on the longus colli muscle anterior to the carotid tubercle. The average distance of the trunk from the lateral margin of this transverse process was 0.50 cm. on the right and 0.44 cm. on the left (Fig. 2). This measurement ranged from 0.1 to 1.2 cm. The average distance of the lower pole of the superior cervical ganglion from the middle of the sixth cervical transverse process was 4.87 cm. on the right and 4.73 cm. on the left (Fig. 2). This distance varied from 3.9 to 6.9 cm. on the right and from 3.2 to 6.0 cm. on the left. In 50 of the 66 dissections, the anterior tuberosity (carotid tubercle) of the sixth cervical vertebra was more prominent than the anterior tuberosity of the fifth cervical vertebra. In the remainder, either the process of the latter segment was the larger or they were so nearly equal in size that either might have been palpated with equal ease. It is recommended that the injection be done at the level of the most easily palpable tuberosity.

It is evident from the anatomic data collected that the tuberosities of the transverse processes of the fifth and sixth cervical vertebrae are ideal landmarks to utilize in blocking the sympathetic impulses to the head. The trunk at these levels may be approached from a point immediately anterior or just posterior to the sternocleidomastoid muscle. The former may be referred to as the anterior and the latter as the anterolateral approach to the cervical sympathetic trunk. In practice it has been found that the anterolateral approach usually is more satisfactory. The reverse may be true if the sternocleidomastoid muscle is exceptionally wide and well developed. The injection is facilitated by having the patient assume the supine position with the head flexed and turned slightly to the opposite side. This makes the bony landmarks easily accessible to the palpating finger even in an obese person. Flexion of the head increases the ease with which the carotid sheath and its enclosed vessels and nerves may be retracted and diminishes the discomfort of deep palpation in this region. Thus, the sympathetic trunk is made readily accessible to injection without danger of penetrating the vessels of the neck or the more medially located trachea, esophagus and thyroid gland.

In a slender patient the entire procedure may be performed with a small hypodermic needle or only a skin wheal may be made with this type needle followed by insertion of a 21 gage venous puncture needle. The skin wheal usually is made along the posterior border of the sternocleidomastoid muscle opposite the fifth or sixth cervical transverse process. The needle is then inserted and advanced until it is in contact with the lateral surface of the tip

of the transverse process, then withdrawn slightly and reinserted along the anterior surface of the tuberosity (Fig. 5). The injection is performed at a depth of approximately 0.5 cm. from the lateral extent of the transverse process. Needless to say, prior to injection, aspiration should be attempted to ascertain that a blood vessel or the subarachnoid space has not been entered. Owing to the oblique direction of the intervertebral foramen in the cervical region, it is practically impossible to insert a needle into the subarachnoid space from the site of injection along the posterolateral border of the sternocleidomastoid muscle unless it is directed upward as well as medially. This need never be done. It is much more likely that this space might be entered by the anterior approach. In either case the importance of preliminary aspiration should never be forgotten. The injection may be done, but usually with less ease and with more discomfort to the patient by retracting the sternocleidomastoid muscle and the carotid sheath and its contents laterally, and the trachea or larynx, esophagus and thyroid gland medially. Blocking the cervical sympathetic trunk by this anterior approach, as well as by the anterolateral approach, is made easier by performing the injection at the level of the most prominent tuberosity on the anterior surface of the cervical transverse processes. At either level and with either approach the most important step in the entire procedure to insure a successful injection is that the bony landmark be well identified with the palpating finger before the needle is inserted. A typical Horner's syndrome usually appears after injection of from 3 to 5 cc. of a one per cent solution of procaine hydrochloride. However, to prolong interruption of the sympathetic impulses, 8 to 10 cc. may be injected. If the latter quantity is used, it is not advisable to do a bilateral block because there may be dyspnea and palpitation due to some infiltration of the phrenic and vagus nerves.

This technic has been used approximately 350 times on a total of 205 patients over a four year period and rarely has it failed to produce a well defined Horner's syndrome. Also in no instance has there been a sequel of any significance. Occasionally, a patient will complain of pain when the needle is inserted because of irritation of a nerve of the cervical or brachial plexus. Hoarseness, due to concomitant infiltration of the recurrent laryngeal nerve, is encountered infrequently. It should be remembered that the injection may cause a slight tissue reaction, and after three or four infiltrations, if fairly large quantities of the anesthetic agent have been used, the patient is likely to complain of soreness about the site of injection. The local increase in vascularity accompanying the inflammatory reaction, as well as the hypertrophy of adjacent lymphoid tissue, may slightly complicate a surgical procedure on the cervical portion of the sympathetic trunk if this follows a series of injections.

In conclusion, it may be stated that infiltration of a suitable anesthetic agent about the sympathetic trunk at the level of the tuberosities of the fifth

or sixth cervical transverse processes is an effective means of blocking the sympathetic impulses to the head. This can be done by the anterior or anterolateral approaches as described. The latter has been found to be more generally satisfactory.

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# ON THE USE OF N. MUSCULOCUTANEOUS FOR NEUROTIZATION OF N. RADIALIS IN CASES OF VERY LARGE DEFECTS OF THE LATTER\*

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WHILE STUDYING THE OPERATIVE TECHNIC which could be used in cases of large defects of the *n. radialis*, we first devoted our attention to the development of a practical method of transposition of the ends of the nerve on the anterior surface of the arm beneath the *m. biceps*. This method of transposition enabled us to repair defects up to 6 cm. (Lurje, 1947).

In the course of such operations we had to place ends of *n. radialis* in the interstitial space between *m. biceps* and *m. brachialis* and in this operative field the musculocutaneous nerve was always seen below the point where it supplies *m. coracobrachialis* and gives off branches to *m. biceps*. In the middle of the arm the nerve gives off its more or less constant large upper branch to *m. brachialis*. We often observed that in the lower half of the arm, *n. musculocutaneus* gave off also 1-2 branches to *m. brachialis* and 1 or 2 small branches to *m. biceps* (the latter less constantly). In the elbow bend, laterally from the bicipital tendon, musculocutaneous nerve occasionally gave off the lower thin branch to *m. brachialis* and then became *n. cutaneus antibrachii lateralis* of the forearm. Because of considerable difficulty in stretching the ends of the *n. radialis* which have been transposed onto the anterior aspect of the arm, and being in doubt whether the central end of the nerve would be able to neurotize its peripheral end due to considerable tension, we have twice decided, in addition, to implant brachial branches of *n. musculocutaneus* into the peripheral end of the *n. radialis*. No technical difficulties were encountered in performing the implantation. Sections of *n. musculocutaneus* immediately below the origin of the main branches to *m. biceps* and above the lower branches to *m. brachialis*, does not affect considerably the active flexion in the elbow. This nerve can therefore be used as a neurotizer (nerve donor) in the lower half of the arm without further essential impairment to motor function. *M. biceps*, with its nerve supply intact, compensates entirely the lost function of the denervated part of *m. brachialis*. This consideration led us to believe that *n. musculocutaneus*, after being sectioned in the indicated place, can be used for neurotization of *n. radialis* by end-to-end suture, in cases of very large defects of the latter nerve which are located in the upper two-thirds of the arm and higher up in the axilla, when the method of transposition of the ends of *n. radialis* onto the anterior aspect of the arm cannot be used in dealing with diastasis. It is essential for the above operation that the upper end of the peripheral section of *n. radialis* be located not less than 6-7 cm.

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above the external condyle of the humerus. Under such circumstances implantation end-to-end of *n. musculocutaneus* into the peripheral section of *n. radialis* can be accomplished without any tension if the *n. radialis* is first brought out between the fibres of *m. brachialis* into the interstitial space between the latter and *m. biceps*.

Anatomic studies carried out in the department of topographic anatomy (Director: Prof. Richter) showed that the branches of *n. musculocutaneus* in the space between *m. biceps* and *m. brachialis* in the lower half of the arm arise at varying levels. One large branch is given off to *m. brachialis* fairly constantly at the level of the middle of the arm or a little higher. This substantial branch can be isolated, if necessary sectioned as low as possible, and used as such for implantation into the peripheral end of *n. radialis*, especially when *n. musculocutaneus* in its lower section gives off only a few motor fibres to *m. biceps* and *m. brachialis*.

During the operation it is therefore desirable to examine *n. musculocutaneus* as far upwards as the borderline between the upper and middle third of the arm, in order to obtain a clear picture of the type of its branching and to determine what motor elements can be used for neurotization of *n. radialis*. This examination should be accomplished without excessive skeletization of the nerve or destruction of its relations with the adjacent tissues and with full preservation of its blood supply. Since large defects of *n. radialis* usually occur in the middle third of the arm where the nerve lies close to the bone, the peripheral end of the nerve in most cases is long enough for a successful operation. It should be pointed out that in cases of large defects of *n. radialis*, operative technic requires the use of two incisions in order to make possible the isolation of both ends of the nerve. The first incision, described by Richter, is made in the upper third of the arm on its internal surface—for isolation of the central end of the nerve and estimation of the extent of the defect. The second incision is made along the brachioradial groove on the external surface of the arm in its middle and lower third. Having established that the defect of *n. radialis* is very large, from the external incision we separate the biceps from the brachialis and isolate the trunk and branches of *n. musculocutaneus*, divide it in accordance with the indications and conditions as outlined above. Neurotization of the freshened peripheral end of *n. radialis* after it has been first exposed in the brachialradial intermuscular groove is then performed. Atrophy of the peripheral end of the *n. radialis* diminishes somewhat a disproportion between the cross-sections of the nerve-recipient and nerve-donor. A large number of sensory fibres in the latter should not influence considerably its capacity to neurotize the nerve-recipient with motor elements. In the process of regeneration nerve fibres give growth to a large number of collaterals. Experimental data of Kilvington, Kennedy, Feiss, Aird and Naffziger show that thinner nerves being sutured with their central ends into the peripheral ends of the thicker

nerves are capable of giving good neurotization of the latter with full restoration of their motor function.

Implantation of the musculotaneous nerve into *n. radialis* has been performed by us in four cases. Two cases suffered shot wounds; these patients came for treatment after having been operated unsuccessfully in other institutions. In one case there was a subcutaneous rupture of *n. radialis*, and the other patient had a rupture of the nerve with open fracture of humerus.

Two cases are particularly interesting.

**Case No. 1.** (demonstrated at the conference of the Neurosurgical Institute A. M. N., March 8, 1947). Patient S., 20 years old. Entered the Institute October 25, 1945. Was wounded March 22, 1944, in the left arm with open fracture of the humerus. A "wrist-drop" developed immediately after the injury, extension in the radiocarpal and metacarpophalangeal joints was lost. Soon afterward causalgia also appeared with predominant



FIG. 1.



FIG. 2.

FIG. 1 and 2. Demonstrating appearance of extension in radiocarpal joint eight months following removal of third thoracic sympathetic ganglion on left side.

localization in the zone of innervation of *n. ulnaris*, while the motor function of the latter remained unaffected. During 1944 three operations were performed on the arm; a fourth operation was a denudation and alcoholization of *n. ulnaris* in the forearm, and a fifth operation was a neurotomy and neurexairesis of *n. ulnaris* at the level of the radiocarpal joint. In spite of all the above operations, causalgia persisted and the clinical picture became complicated with a paralysis of the distal branches of *n. ulnaris*.

Operation (Lurje) Nov. 4, 1945. First incision—18 cm. long—was made on the external surface of the arm with continuation onto the brachio-radial furrow. *M. biceps* and *m. brachialis* were drawn aside from *m. triceps*. In the lower part of the incision only the peripheral end of *n. radialis* was found. Another incision—20 cm. long—was made on the inner side of the arm from *m. pectoralis major* to the lower third of the arm. In the upper part of the wound the central neuroma of *n. radialis* was found. The defect of the nerve was so large that it could not be repaired by the method of transposition of

its two ends onto the anterior surface of the arm. *N. musculocutaneus* was exposed, its function was tested electrophysiologically, and then it was divided distal to the origin of its principal branches to *m. biceps*, but proximal to the origin of several rather conspicuous branches to *m. brachialis*. The central end of the *n. musculocutaneus* was implanted into the freshened peripheral end of *n. radialis*. In addition a denudation of the brachial artery was performed extending through the whole medial incision. Both incisions were closed in layers.

In spite of denudation of the brachial artery the causalgic pains re-appeared three days after the operation. July 1, 1946 the patient was admitted into the Yauza Hospital Medsantrud with persistent causalgic pains. Examination revealed that *m. brachio radialis* had begun to contract. On July 12, 1946 the third thoracic sympathetic ganglion was removed on the left side (Lurje); and thereafter causalgic pains disappeared entirely. In February, 1947 extension in the radiocarpal joint began to appear and was quite good when the patient was examined on March 7, 1947 (see Figs. 1 and 2). Extension in the metacarpo-phalangeal joints was not restored. Paralysis of the distal branches of *n. ulnaris* persists.

**Case No. 2.** Patient L., 22 years old, was wounded March 28, 1944 with injury of humerus and *n. radialis* on the left side. Had undergone three previous operations for osteomyolitis of the humerus, at one of the hospitals in Moscow. Another operation was performed for paralysis of *n. radialis*, whereby a large defect was found and this was replaced with section taken from the peripheral end of the nerve dissected longitudinally. The patient was admitted into the Medsantrud Hospital April 9, 1946 with a picture of paralysis *n. radialis* without any apparent symptoms of regeneration. Operation April 17, 1946 (Lurje). *N. radialis* was exposed from two incisions, one on the inner and the other on the outer side of the arm. There were large scars and complete cicatricial degeneration of the transplanted nerve tissue; there was a neuroma on the central stump of the injured nerve. After the ends had been freshened, the defect was so large that direct neuropathy with transposition of the nerve ends onto the anterior surface of the arm was impossible. *N. musculocutaneus* was sectioned above the origin of two branches to *m. brachialis* and its central end implanted end-to-end into the peripheral end of *n. radialis*.

Examination on May 5, 1947 revealed presence of active contractions of *m. brachio radialis* and appearance of slight extension in the radiocarpal joint.

These two cases demonstrate that neurotization of *n. radialis* by implantation into it of *n. musculocutaneus* can be performed with clinical success in cases of large defects of the former if a sufficient length of the peripheral end of *n. radialis* remains available in the arm, and this can be achieved without seriously impairing the principal function of the musculocutaneous nerve, namely, flexion of the elbow.

We believe that neurotization of *n. radialis* with *n. musculocutaneus* becomes particularly important when large defects in the former are accompanied by injury of the median and ulnar nerves. In such a case, the plastic operation on tendons, according to Pertes and Tichonovich, as it is done in cases of isolated injury to *n. radialis*, cannot be performed successfully. Chaklin regards good function of the median and ulnar nerves, as well as of all muscles innervated by these nerves and of all joints of the wrist and fingers, as the criterion for success of plastic operation on tendons. Therefore, in patients such as our Case No. 1, where there was paralysis of both *n. radialis* and of *n. ulnaris*, our operation was especially indicated as it is capable of restoring active extension of the wrist.

In the course of usual healing of the nerve wound with secondary neurorrhaphy, the nerve fibres regenerate twice: the first regeneration leads to formation of the neuroma and only repeated regeneration, which follows suturing the freshened ends, results in neurotization of the peripheral segment.

In the operation of implantation of *n. musculocutaneus* into *n. radialis*—as in the other similar heterotopic operations—fresh neurotizing fibres were introduced into the peripheral section of the injured nerve. The good regenerative potency of these fibres is immediately realized in the biologically fully prepared bed of the peripheral end of the nerve. When the defect of *n. radialis* is situated high up, the implantation described here, being performed below the zone of trauma and scarification, will be undertaken under the “ideal” conditions for regeneration, since the zone of the nerve suture will be surrounded by healthy and not scarified tissues. It is well known that the regenerative capacity of the axons of the central end and of their cells diminishes if a considerable time elapses after the trauma (Foerster, Egorov, Chubumaher, Bondarchuk), and particularly so with repeated operative interventions. Therefore, neurotization of the injured nerves with freshly cut nerves should be attempted only when local anatomical conditions permit. Both our patients were operated relatively late (19 and 25 months) after trauma and the regeneration obtained should diminish our pessimism regarding late restorative operations on the nerves.

Sometimes conditions arise which indicate a high implantation of *n. musculocutaneus* into *n. radialis*. This can be performed when large and irreparable defects are present in these nerves in the pectoral region if the central section of the musculocutaneous nerve is sufficiently long. The latter can then be implanted into the peripheral section of *n. radialis* if it is technically possible. The patient would, of course, lose flexion of the elbow, if the median nerve does not give accessory branches to *m. biceps* and *m. brachialis* lower in the arm. In performing such implantation we first split the peripheral end of *n. radialis* and separate from its main principal trunk the branches to *m. triceps* and also cutaneous rami to the dorsum of the arm and forearm, which all lie together with the main trunk within the common epineurial sheath. The central end of the musculocutaneous nerve is then implanted into the trunk of *n. radialis*. In the presence of paralysis of *n. musculocutaneus* neurotization of the branches to the triceps is not important as the patient will have to use an apparatus fixing the forearm at a 90° angle to the arm. Furthermore, separation of the above branches makes the cross-sections of the nerve-donor and nerve-recipient more comparable. Such an operation has been performed in the Medsantrud Hospital April 19, 1947 (Prof. Lampert and Lurje) on a 55 year old patient D. After removal of a tumor (neuroma type) large defects resulted in the musculocutaneous nerve and in *n. radialis*, which were imbedded in the tumor, while the central end of the former nerve was sufficiently long to permit its implantation into the peripheral end of *n. radialis*.

### CONCLUSIONS

1) In cases of very large defects of *n. radialis*, which are located in the upper two-thirds of the arm and in the axillary region, *n. musculocutaneus* can be employed for neurotization of the injured nerve.

2) *N. musculocutaneus* should be sectioned below the origin of the principal branches to *m. biceps* and above the origin of the branches to *m. brachialis* and then its central section implanted end-to-end into the peripheral section of *n. radialis*.

A definite regeneration of *n. radialis* has been obtained in two cases after implantation into this nerve of *n. musculocutaneus*.

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# THE USE OF MECHANICALLY WOUND BOBBINS FOR HANDLING AND DISPENSING NON-ABSORBABLE SUTURE MATERIAL, WITH OBSERVATIONS ON THE TENSILE STRENGTH AND STERILITY OF MECHANICALLY WOUND SUTURE MATERIAL \*

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IT IS THE GENERAL SURGICAL PRACTICE to prepare non-absorbable suture material for sterilization by hand, winding small lots on rubber tubing, glass rods, cardboard, rubber-edged wooden boards, or as loose skeins. At the operating table it is the nurse's duty to prepare from these lots single strands of suitable length for sutures and ligatures. Some surgeons, when tying a series of ligatures, reel off the required lengths from a previously wound tube or rod held in the hand.

The cumbersome and time-consuming nature of these techniques has prompted the trial of metal bobbins, bobbin cases, and a motor driven bobbin winder. It was felt that long lengths of non-absorbable suture material could be quickly wound on metal bobbins using a motor driven winder, both bobbins and winder being of the types ordinarily used on domestic sewing machines. These winders and bobbins were secured from local sewing machine dealers.

A fractional horse-power motor was equipped with a rubber stopper on the shaft to serve as a friction drive for the bobbin winder, (Fig. 1) and the bobbin winder was arranged so that it could be engaged or disengaged from the driving wheel at will. A spindle to hold the spool of suture material and a guide for the suture material were added. The only tension on the suture material while being wound on these bobbins was the friction of the spool on the spindle and the suture material passing through the guides. In one assembly, grinding and polishing wheels were incorporated for use in sharpening and polishing hollow or surgeons' needles (Fig. 2).

The metal bobbins used are 33 mm. long with 9 mm. flanges on the ends, (Fig. 3-C) and were also purchased from sewing machine dealers. They are probably made of brass plated steel.

The cases to hold the bobbins served as suture dispensers, and two types have been used to date. One type, (Fig. 3-A) of stainless metal was made for us by the American Hospital Supply Corporation through the kindness of Mr. E. H. Blount of their Atlanta office. It is 6.0 cm. long and 1.5 cm. in outside diameter and allows sufficient room within it for the bobbin to rotate and also move longitudinally as suture material is being dispensed through the slot cut in one side. Holes are drilled in each end to facilitate sterilization.

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The other type of case and suture dispenser (Fig. 3-B) is made of black phenol formaldehyde molding material and were secured from the Wheeling Stamping Company in Wheeling, W. Va. These are 6.5 cm. long and 1.5 cm. outside diameter and, after purchase, a slot was cut in one side and a hole

FIG. 1.

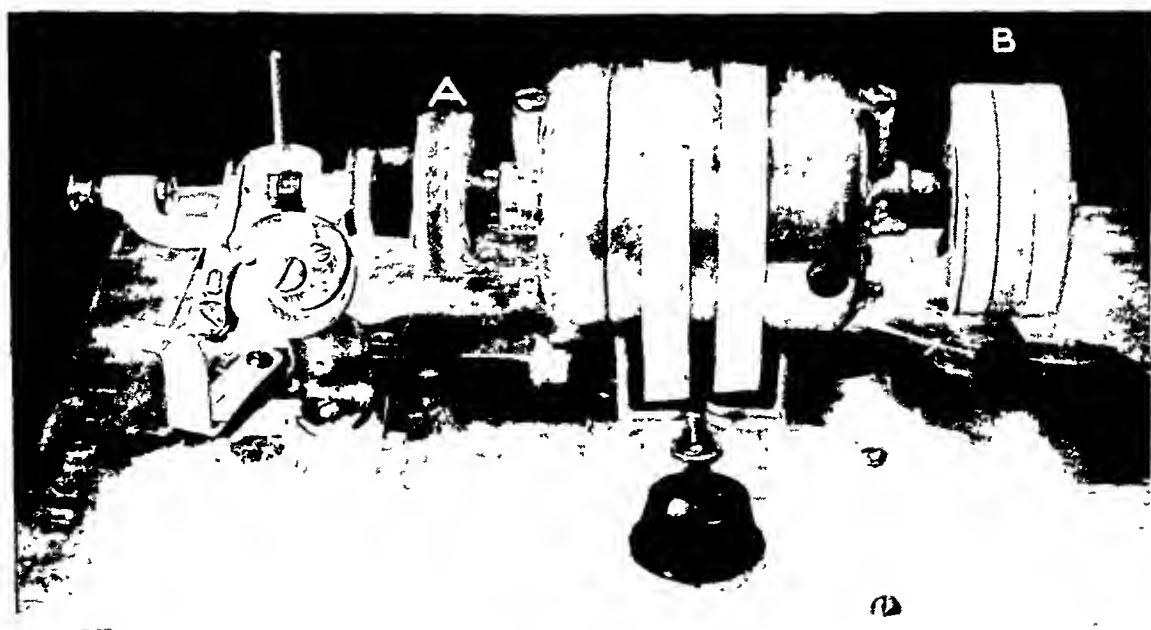
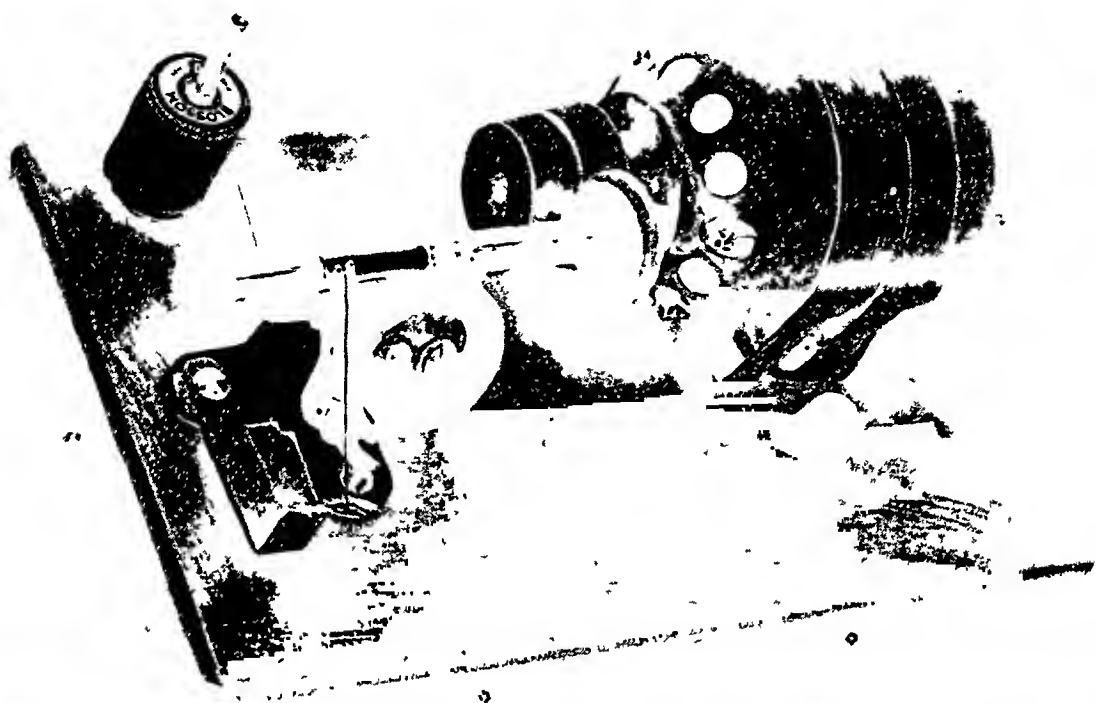


FIG. 2.

FIG. 1.—One type of motor driven bobbin winder. FIG. 2.—A type of motor driven bobbin winder incorporating a wheel (A) for polishing surgeon's or hollow needles, and a grinding wheel (B) for sharpening needles.



drilled in each end. These cases have not been harmed by countless trips through the autoclave.

In considering the clinical use of this equipment, attention had to be given to two important factors:—

1. Alterations in tensile strength
2. Sterility of non-absorbable suture material after it was wound mechanically on these metal bobbins and either boiled or autoclaved.

Experiments were then carried out to study these two factors.



FIG. 3.—Types of bobbins and bobbin cases used. The stainless steel case is shown at (A) the case of phenol formaldehyde molding material at (B). The bobbins used are shown at (C).

#### STUDIES ON TENSILE STRENGTH OF NON-ABSORBABLE SUTURE MATERIAL AFTER WINDING AND STERILIZING ON MECHANICALLY WOUND BOBBINS

Meade, Ochsner, Dixon and Long<sup>1, 2, 3, 4</sup> have given repeated warnings that the tensile strength of cotton will be appreciably impaired if the materials are boiled or autoclaved under any tension, as when wound on wood, glass, metal or even rubber tubing, which does not allow enough slack for normal shrinkage. Localio, Casale, and Hinton,<sup>7, 8</sup> who stated that cotton loses strength during sterilization, were criticized by Thorek<sup>6</sup> because they based their conclusions on samples sterilized on mechanically wound bobbins.

Mr. Frank R. Redman,<sup>5</sup> a well known consultant to the textile industry, feels that from his own experience boiling and autoclaving temperatures do not harm cotton fibres and have no effect on the strength of cotton thread if the thread is not held under tension while at the elevated temperature. He ex-

plained that during the original spinning of the yarn there is some tension which elongates the yarn by deforming the fibres. When this new thread is heated under tension the fibres become soft, thereby losing their grip and making the thread weaker. If, however, there is minimal or no tension during heating, the fibres return to their original shape and become interlocked to a greater extent than before heating. He suggested that if the thread is wound very loosely on the bobbins, there would be enough slack to allow the fibres to return, i.e., shrink, to their natural state, and the strength of the thread would not be impaired and might even be increased.

In view of these reports, experimental studies were carried out on several types of suture material to determine how much, if any, was the difference in tensile strength between non-sterile control samples, control samples sterilized after winding loosely on gauze, and test samples sterilized after winding on bobbins.

For the cotton materials, this study was also, in effect, a rough quantitative test determining whether the tension of the bobbin-wound materials was enough to prevent normal shrinkage and thereby to weaken the thread.

#### MATERIALS AND METHODS

The materials tested were: No. 40 J and P Coats six cord plain cotton, No. 60 J and P Coats six cord plain cotton, No. 60 Blossom mercerized cotton, No. A Belding-Corticelli black twisted silk, and No. 4-0 serum proof braided silk (Deknatel), all purchased on the open market.

From each sample, testing was carried out on ten or more consecutive strands of 30 to 40 cm. in length. The upper end of each strand was wound around a cylindrical bar and the lower end around a horizontal spool holding a basket for weights. In this way the free strand was between 10 and 20 cm. in length and was attached at each end to a smooth surface with no acute angles. A basic initial weight pull of well below the breaking strength was determined for each sample before recordings were made. Each test was started by gently attaching the basic weight to the lower end of each strand and allowing it to hang freely, but not untwisting for 15 seconds. Then increments of 20 Gm. were added every five seconds until the strand broke.

Control readings were taken on samples directly from each spool. Samples of each material were then wound on gauze and on a bobbin before sterilizing. Separate samples of each were sterilized respectively by boiling 20 minutes, 30 minutes, one hour and two hours, and by autoclaving one, two, and three times at the usual temperature of 250°F. (15 pounds pressure) for a minimum of 15 minutes each. Those autoclaved more than once were allowed to cool and dry before re-autoclaving, and all samples were tested dry.

Since the knot is the weakest part of any suture, as shown by Taylor,<sup>9, 10</sup> readings were also taken on knotted strands of each sample. Each strand was cut in half and then tied with a single square knot snugly by hand before the weights were added. Invariably the strand broke at the knot. Occasionally the

	Mean tensile strength and standard deviations in grams of suture materials sterilized on gauze and on bobbins.	N = number of observations, which is 10 unless otherwise noted.	t = value of t in Student's t-test for unique samples.	S1 = Significant difference at 1% level	NS = Not significant at 5% level
(For N <sub>1</sub> + N <sub>2</sub> - 2 = 18, t = 2.878)	.806 NS	10	1.93 NS		
(For N <sub>1</sub> + N <sub>2</sub> - 2 = 18, t < 2.101).	.806 NS	10	1.93 NS		
* = See comments in text.					

# MECHANICALLY WOUND SUTURES

twisted black silk knots slipped out with the basic weight, and these strands were discarded.

## RESULTS

The mean breaking strengths with their respective standard deviations to the nearest whole number are recorded in Table I. These results are tabulated for each sterilizing treatment in pairs representing the gauze-wound control sample and the bobbin-wound test sample. The difference between the means and also the *t* value\* for the significance of this difference is recorded beneath each pair, with letters denoting whether this difference is of no significance at the 5% level (NS), of significance at the 5% level (S5), or of significance at the 1% as well as the 5% levels (S1). The differences are noted as positive (+) if the bobbin-wound mean was larger than the gauze-wound control mean, and as negative (—) if the bobbin mean was smaller than the control mean.

CHART I-A

CHART I-B

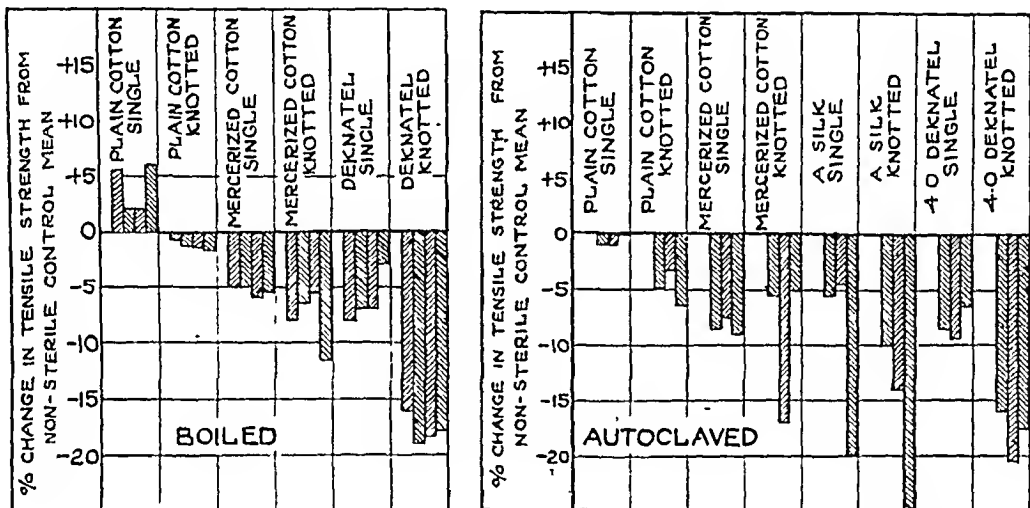


CHART I-A.—Average changes in tensile strength due to boiling. Computed from Table I. Reading from left to right in each group of cross-hatched columns, the columns indicate respectively the per-cent changes in tensile strength after boiling for 20 minutes, 30 minutes, one hour and two hours. I-B.—Average changes in tensile strength due to autoclaving. Computed from Table I. Reading from left to right in each group of cross-hatched columns, the columns indicate respectively the per-cent change in tensile strength after autoclaving once, twice and three times.

For reasons to be discussed later the significantly different pairs have been classified into two groups, those significant at the 5% level and those significant at the 1% level as well as at the 5% level. The “5% level” of significance denotes that the odds are at least 95:5 (19:1) that the difference between the means did not occur by chance. The “1% level” denotes that the odds are at least 99:1 against chance.

Of the differences between means in the 63 pairs reported, 48 (or 76%)

\* The *t* value is a ratio of the difference between the means to the standard error of this difference, with suitable corrections being made for the small number of strands tested in each sample.<sup>11</sup>

were not significant and 15 were significant at the 5% level. Of these 15 pairs with significant differences ten of the bobbin-wound samples were stronger and five were weaker than their respective gauze-wound controls. Only eight of the 63 pairs showed significant differences at the 1% level, and of these, five of the bobbin-wound samples were stronger and three were weaker than their controls.

With the knotted strands, in only three of 31 pairs were there significant differences between the means, the bobbin-wound samples being stronger than their controls. In all 63 pairs, and disregarding significances, the bobbin-wound materials were stronger in 36 and weaker in 27 than their respective gauze-wound control materials.

The standard deviations for single strand non-sterile controls ranged from 25 Gm. for twisted silk to 60 Gm. for No. 40 plain cotton. For single strands sterilized on gauze the standard deviations ranged from 13 Gm. for twisted silk to 82 Gm. for No. 40 plain cotton. For those sterilized on bobbins, the range was essentially the same, i.e., from 13 Gm. for twisted silk to 86 Gm. for No. 40 plain cotton.

With the knotted strands the standard deviations were generally higher and covered a larger range. For the non-sterile controls they ranged from 36 Gm. for the twisted silk to 65 Gm. for No. 60 plain cotton. For those sterilized on gauze, deviations ranged from 31 Gm. for No. 40 plain cotton to 121 Gm. for the same material. For those sterilized on bobbins, deviations ranged from 27 Gm. for No. 40 plain cotton to 103 Gm. for No. 60 mercerized cotton.

The observed data incidentally shows the effects of knotting and of repeated sterilizations on tensile strength with exclusion of the factor of bobbin winding.

A comparison of the mean strengths of samples tested single and knotted but otherwise treated the same way showed consistent and significant weakening of the knotted strands. The percentages of loss of tensile strength are summarized in Table II. The smallest percentage loss was with No. 60 mercerized cotton, the average being 21% with a range of 9 to 32%. The greatest loss was with No. 60 plain cotton, the average being 28% with a range of 16 to 40%. The over all average in 60 comparisons was 25% with a range of 9 to 40%.

Comparisons of the mean tensile strengths of sterilized materials with the strengths of their respective non-sterile controls were analyzed for significant differences. For the sake of brevity, only a few representative figures are recorded in Table I adjacent to the spool control values. Number 40 plain cotton tested single showed a consistently significant increase after sterilization, but the same material knotted and the mercerized cotton showed decreases in strength. The No. 60 plain cotton varied above and below the control value, but was equal to or less than the control in all autoclaved samples. Black twisted silk lost strength rapidly with repeated autoclaving. The serum-proof

braided silk lost strength with the initial sterilization but subsequently showed no appreciable changes.

Chart I is a composite summary of per cent changes due to sterilization. Boiled plain cotton showed a tendency to increase in strength. Mercerized cotton and both types of silk showed decreases mentioned above. All knotted sterilized samples showed decreases from the knotted non-sterile controls. This was especially so with both types of silk.

#### SUPPLEMENTARY STUDIES AND RESULTS

It will be noted that the non-sterile control mean for No. 40 plain cotton was obtained from 40 strands. The first 20 of these strands showed a mean breaking strength of  $1069 \pm 50$  Gm. The other 20 strands were taken from the last portion of the same spool and showed a mean strength of only  $1027 \pm 62$  Gm. The difference between the means is 42 Gm., and  $t$  equals 2.35, which denotes a significant difference at the 5% level but not at the 1% level. In this case the mean of all 40 strands  $1048 \pm 60$ , has been recorded in Table I.

The significantly different pair of No. 60 plain cotton autoclaved one time was repeated twice with new samples each time. The means for one pair were gauze  $894 \pm 40$  Gm., bobbin  $866 \pm 57$  Gm., and for the other,  $964 \pm 54$  Gm., bobbin  $930 \pm 59$  Gm. There is no significant difference within each pair, but a highly significant difference between each gauze-wound control.

The mean reading for 10 strands of serum-proof braided silk autoclaved two times on gauze was computed and has been recorded as  $840 \pm 41$  Gm., being 90 Gm. less than the bobbin-wound mean. Additional readings were then made on the 7 remaining consecutive strands from the same gauze-wound skein. The mean proved to be  $980 \pm 24$  Gm., which is significantly different at the 1% level from the first 10 strands and also from the bobbin-wound sample. However, the mean of all 17 strands was  $898 \pm 80$  Gm., which is not significantly different from the bobbin mean of  $930 \pm 27$  Gm. On the other hand, four additional unsterile and two additional boiled gauze-wound control tests made from a new spool of the same size and brand of serum-proof braided silk showed respectively no significant differences even at the 5% level.

#### COMMENT

It is generally conceded that the 5% level of significance between differences is strict enough for critical analysis. We have pointed out that, of the differences in mean tensile strength of 63 comparable pairs of gauze-wound and bobbin-wound suture materials, only 15 were of significance at the 5% level, and that of these, the bobbin-wound materials were stronger in 10 and weaker in 5.

In view of the fact that the analysis of the non-sterile control figures of No. 40 plain cotton showed that cotton from the same spool could vary significantly at the 5% level, the more strict test of significance at the 1% level was also applied. With this test only 8 pairs showed a significant difference, and of these the bobbin-wound materials were stronger in 5 and weaker in 3.

In summary, then, 76% of the tests showed no significant differences at the 5% level, and 87% showed none at the 1% level. Of the cases where significant

differences were demonstrated, the bobbin-wound materials were stronger than the gauze-wound ones in a ratio of about 2:1, which is of no significance in the over all analysis, because in the 63 pairs the bobbin mean was stronger in 36 and weaker in 27, a ratio of only 4:3.

We conclude, therefore, that winding suture materials without tension on these bobbins prior to routine sterilization has no appreciable effect on the ultimate tensile strength of the sterilized materials. And, in the case of cotton, the tension with which it was wound on the bobbins was not enough to prevent normal shrinkage.

An explanation for the presence of the demonstrated significant differences is suggested by the supplementary studies. The repeated studies on the No. 60 plain cotton autoclaved one time showed a significant difference between the two gauze-wound samples. This suggests that the significant difference in the original study was due to the variability of the cotton within Lot A, just as the demonstrated difference between the non-sterile controls of Lots A and B was also significant.

In the repeated study of an entire 25 yd. spool of No. 4-0 serum-proof braided silk, we found no significant variation in tensile strength. This suggests that the samples used for the original study were picked by chance from a non-uniform lot of material.

In other words, we believe that the demonstrated significant differences between the means of consecutive strands receiving the same treatment in these experiments were probably due to lack of randomness in sampling rather than to the effect of winding on bobbins.

The average decrease in tensile strength of 25% due to knotting alone confirms the work of Taylor and others that knotted strands are weaker than straight single strands. Of course, the human factor in the tying of the knots may partially account for their observed larger standard deviations and differences between means.

As regards the effects of sterilization alone, our observations show a tendency for plain cotton to increase in strength if boiled, but to change little if autoclaved. This is in agreement with the theoretical prediction of Redman previously mentioned, and along with the decrease shown in silk the figures generally confirm the work of Ochsner, et al.<sup>1, 2, 3, 4</sup>

No attempt has been made to study all types and brands of non-absorbable suture material. These studies would indicate that for the materials used, the strength of the same size and brand may not only vary from spool to spool, but even vary significantly on the same spool.

All who have used cotton for sutures have the clinical impression that its tensile strength varies widely. From these studies, it appears that within the limits of routine practice, the variability in the cotton itself<sup>8</sup> and its high coefficient of friction<sup>4, 10</sup> are more likely causes of breakage at the operating table than are the time of sterilization and the tension under which the cotton was wound.

Repeated autoclaving or boiling of unused bobbin-wound cotton is not recommended. The possibility of actual weakening through rot or mildew would be present if either gauze-wound or bobbin wound material were contaminated and stored while wet. Furthermore, we have found that rust from the bobbin shaft often stains the inner portion of the thread if it is not used within a reasonable length of time after autoclaving. This latter objection might be overcome by storing sterile bobbin-wound materials in antiseptic solutions fortified with a reducing agent, such as sodium nitrite, or by using bobbins made of or plated with a non-corrosive metal.

STUDIES ON STERILITY OF NON-ABSORBABLE SUTURE MATERIAL AFTER WINDING  
AND STERILIZING ON MECHANICALLY WOUND BOBBINS

When wound with the motor-driven winder, each bobbin could hold ten to fifteen layers of suture material depending on the thickness of the samples used. Controlled studies were carried out to test the sterility of the material after winding bobbins full, placing them in the bobbin cases and subjecting them either to boiling for 30 minutes or autoclaving at 250°F., and 15 lbs. pressure for a minimum of 15 minutes each.

TABLE II.—*Percent Loss of Tensile Strength of Suture Materials  
Due to Knotting of Strands*

(Calculated from Comparable Mean Tensile Strengths Recorded in Table I)

Material	Number of Comparison	Average	% Loss of Tensile Strength Range
No. 40 Cotton, plain.....	15	27	18 - 35
No. 60 Cotton, plain.....	8	28	16 - 40
No. 60 Cotton, Mercerized.....	15	21	9 - 32
No. A Silk, black twisted.....	7	25	21 - 31
No. 4-0 Silk, braided serum-proof...	15	27	19 - 32
TOTAL .....	60	25	9 - 40

TABLE III

	Number Bobbins	Positive Cultures	Negative Cultures
Autoclaved .....	20	0	20
Boiled .....	33	5	28
Controls .....	18	16	2

These experiments were carried out with the kind assistance of Dr. McDonald Fulton, Director of the Department of Bacteriology. He suggested that pure fresh cultures of *B. mycoides* be used since this organism is a spore-former and yet of relatively low pathogenicity when handled.

Each bobbin to be tested was wound with one layer of suture material and then contaminated with a fresh suspension of *B. mycoides* in normal saline. Then twelve to fifteen more layers of suture material were added to the bobbin and each bobbin placed in its case.

These were then divided into three groups—(A) This group was autoclaved as described above. (B) This group was placed in an incubator overnight. (C) This group was boiled for 30 minutes. Following these procedures,



all but the 2 inner layers of suture material were removed from each bobbin and the bobbin was then cultured by dropping it directly into a test tube of infusion broth. All tubes were then incubated for four days. The results of these experiments are shown in Table III. All of the autoclaved materials were sterile, but 5 out of 33 of the boiled materials showed viable organisms still present.

These results lend evidence that autoclaving is a safe way to insure complete sterility of all the suture material on the bobbins, but that boiling should probably not be relied upon for asepsis.

#### SUMMARY AND CONCLUSIONS

1. Sixty-three comparisons of the tensile strengths of various cottons and silks sterilized on gauze and on bobbins are presented. These comparisons have been made on knotted as well as single unknotted strands.

2. The tensile strengths of materials of the same brand and size may vary significantly not only from spool to spool, but on the same spool.

3. In 76% of our comparisons there were no significant differences at the 5% level between the tensile strengths of materials wound loosely on gauze and those wound mechanically on bobbins. In 87% there were no significant differences at the 1% level.

4. Considering the lack of randomness in sampling in these experiments we conclude that winding non-absorbable suture materials on our bobbins with minimal tension prior to routine sterilization has no appreciable effect on the ultimate tensile strength of the sterilized materials.

5. The knotting of a suture decreased its tensile strength on an average of 25%, the material adjacent to the knot being invariably the point of breakage.

6. Plain cotton tended to increase in strength if boiled, but to change insignificantly if autoclaved. Mercerized cotton and serum-proof braided silk tended to lose strength with initial sterilizations, but subsequently showed no appreciable changes with repeated autoclaving. Knotted sterilized strands were in all cases not only weaker than the knotted non-sterile controls but also tended to lose proportionately more strength than the single sterilized strands.

7. Full bobbins, containing approximately 15 layers of suture material should be sterilized by autoclaving rather than by boiling, for there is some question that the latter method effectively sterilizes the innermost layers of the suture material.

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\* The authors are grateful to Edward Patterson for his technical assistance in carrying out these studies.

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# CARCINOID TUMORS OF THE RECTUM

Report of Three Cases, Two with Metastases \*

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## INTRODUCTION

EXCELLENT REVIEWS ON THE SUBJECT of carcinoid, or argentaffin, tumors of the gastro-intestinal tract are readily available.<sup>1, 2, 3, 4, 5</sup> These tumors were considered by early writers to be benign but because of their resemblance to carcinoma have been called carcinoid.<sup>6</sup> Further experience with the lesion, however, has shown that many of the tumors spread to regional nodes and some to more distant sites. It has been found that the incidence of metastases from carcinoid tumors of the small and large intestine is significant. These findings are in contrast to those of carcinoids of the appendix, the common site of the tumor, which show a low incidence of nodal involvement or more remote metastases.

Recently<sup>7, 8, 9, 10</sup> attention has been directed to primary carcinoid tumors of the rectum, previously considered to be a very rare lesion. Up to 1942 Stout<sup>7</sup> found record of only six cases<sup>11-16</sup> and in that year added six of his own. Since then the number has increased so that at present, at least 29 carcinoid tumors of the rectum are on record.<sup>7-18</sup> Only two of these have been associated with distant metastases.<sup>12, 16</sup>

We present three cases of carcinoid tumor of the rectum. All were diagnosed by surgical biopsy, and surgical exploration of the abdomen was performed in two cases. One of these patients (Case 1) showed multiple metastases at operation, died 18 months postoperatively and came to necropsy. The second patient, (Case 2) at operation, showed metastases to the para-aortic nodes, the right perinephric region, and the liver. She refused subsequent operation and treatment, and was living but markedly debilitated, losing weight, and bleeding by rectum six months postoperatively. The third patient (Case 3) had a small rectal polyp removed through a sigmoidoscope. Four months postoperatively he had no further symptoms and was being followed in the surgical out-patient clinic.

## CASE REPORTS

**Case 1 (\*\*).**—C.J.G., a 51-year-old white male entered the U. S. Naval Hospital, Philadelphia, Pa. on November 22, 1943 complaining of weakness and fatigue of two months' duration. Weight loss of about 15 pounds occurred during this period. Tarry stool and decreasing caliber of the bowel movements had been noticed for four months

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\*\* We are indebted to Captain H. H. Montgomery (MC) USN, MOIC, U. S. Naval Hospital, Philadelphia, for permission to use the clinical and autopsy records of this case.

† Formerly, first assistant in pathology, Mallory Institute of Pathology; instructor in surgical pathology, Tufts College Medical School.

prior to admission. The patient had had no bowel movements during the five days before admission. The history was otherwise not contributory and the positive physical findings were limited to the abdomen and rectum. There was mild right upper quadrant abdominal tenderness, the liver edge was felt at the level of the umbilicus, and the left lobe of the liver was said to be nodular. On rectal examination there was a moderately hard, movable, polypoid growth in the posterior wall of the rectum. A few flecks of blood were present on the examining finger. Laboratory examinations of blood and urine were essentially negative, as were roentgenograms of the chest and skeletal system. Barium enema and gastrointestinal series showed no abnormalities of the gastro-intestinal tract. Proctoscopic examination revealed three hard nodular masses on the left and posterior walls of the lower rectum. The nodules were covered by intact mucosa. A punch was inserted through the mucosa and tissue from the tumor obtained for histologic diagnosis. The pathologic report:

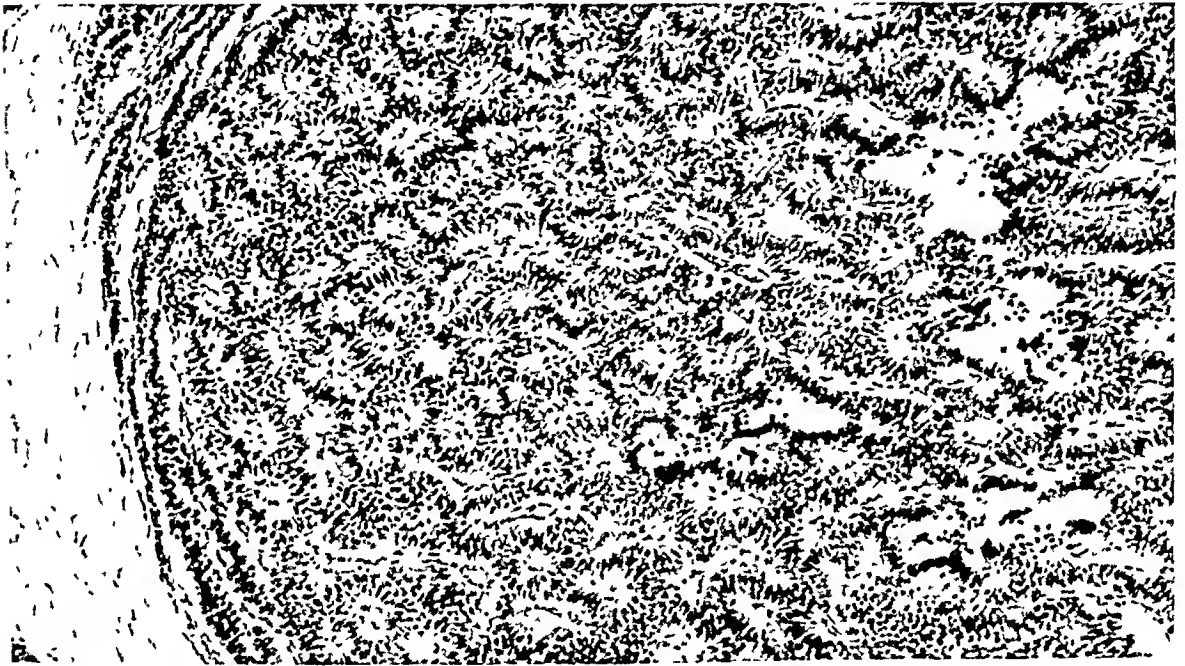


FIG. 1. Case 1.—Festoons of ribbons arrangement of columns of carcinoid tumor cells. Hematoxylin and eosin. (X200)\*

*Gross description.* The specimens are two in number. They are firm, yellow, curled tissue masses, one of which is 5 x 3 x 2 mm. and the other 2 x 2 x 2 mm.

*Histologic description.* The sections consist of a rounded piece of rectal mucosa that for the most part is intact and essentially normal in appearance. Immediately beneath it, and extending throughout the narrow submucosal zone, are solid rounded masses of cells of an indeterminate type but having oval shaped nuclei of uniform size and quality with no hyperchromatic changes. Irregular infiltration of the mucosa has taken place as well as in areas in the deeper portions. The appearance is not that of primary carcinoma of the rectum.

*Diagnosis.* Carcinoid of the rectum. A repeat specimen was requested and at operation two firm tumors beneath the intact mucosa on the left side of the lower rectum were again found. They were movable and not connected. The lower was completely excised. Surgical pathologic report:

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\* We are indebted to Mr. Leo Goodman, Boston City Hospital, for the photomicrographs appearing in this article.

*Gross description.* The specimen consists of a rounded grey-yellow mass  $3 \times 2.5 \times 1.2$  cm. It cuts with a slightly increased resistance and shows a homogeneous grey color throughout.

*Histologic description.* The sections consist of a large rounded mass of tissue covered on one side with intact and essentially normal appearing mucosa. The main substance is made up of compact islands and cords of cells that in places are arranged in a pseudo-acinar pattern. The cells all tend to be of cuboidal and columnar type and they are arranged in a longitudinal pattern without formation of lumens. The nuclei are of uniform size, shape and staining with no hyperchromatic tendencies. Mitotic figures are not seen. There is infiltration of the mucosal stroma and in places the tumor mass extends through the surface epithelium for a short distance. Infiltration of the underlying smooth muscle is noted in the deepest portions and isolated groups of cells are present between the muscle bundles. Silver stains reveal no definite granules in the cytoplasm of any of the tumor cells.

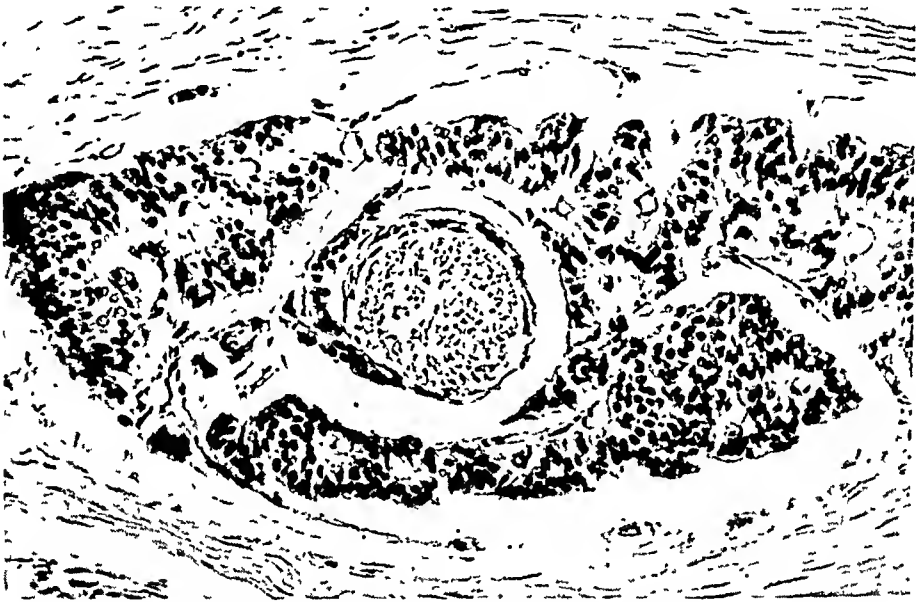


FIG. 2. Case 1.—Perineural lymphatic invasion by carcinoid tumor cells in rectovesical septum. Hematoxylin and eosin. (X400.)

*Pathologic diagnosis.* Carcinoid of the rectum.\*

The patient was treated symptomatically and an abdominal exploration was performed. A small hard mass was palpated in the rectal wall, the liver was enlarged and nodular, and there was a small mass about the size of a marble attached to the lower pole of the right kidney. After a short convalescence, the patient was discharged on Feb. 16, 1944. He slowly lost weight and strength, and the liver and spleen became enlarged. Readmission to the same hospital on Dec. 29, 1944 revealed a red blood count of 2,320,000 per cu. mm. and a hemoglobin of 7 Gm. per 100 cc. The patient died on June 29, 1945 about two years after the onset of weakness and fatigue, symptoms which had been preceded by tarry stools for two months.

*Autopsy report.* (A-45-205, U. S. Naval Hospital, Philadelphia): Only significant findings are presented. The advanced emaciation of the face, thorax, and extremities

\* Both pathologic reports by courtesy of Captain H. M. Dixon (MC) USNR, at that time Chief of Laboratory, U. S. Naval Hospital, Philadelphia, Pa.

contrasted with a tremendously distended abdomen. The sclerae were icteric. The heart and lungs were essentially negative. The peritoneum contained 5,500 cc. of serosanguineous fluid. The liver was very large, weighing 13,200 Gm. The enlargement was generalized, although more prominent in the right lobe. The liver surface was made up of irregular, varying sized nodules from 1 to 20 cm. in diameter. The nodules were generally yellow-white but had hemorrhagic and cystic areas which contained bloody fluid. Section of the liver revealed that most of the organ was replaced by friable and cystic, nodular tumor. The spleen weighed 240 Gm. and was not remarkable. The gastrointestinal tract was completely negative except for the rectum. On the anterior rectal wall, 2 cm. above Hilton's line, there was a smooth somewhat firm area 1 cm. in diameter. The mucosa was apparently intact over the tumor, but between the latter and the bladder there was an irregularly outlined mass of white tissue directly connected to the submucosal tumor mass. Beyond and above this point in the rectovesical tissues, a little to the left of the midline, there were several oval and spherical masses, the largest measuring 1.4 cm. in diameter. These were firm and white or olive drab in color and one showed some

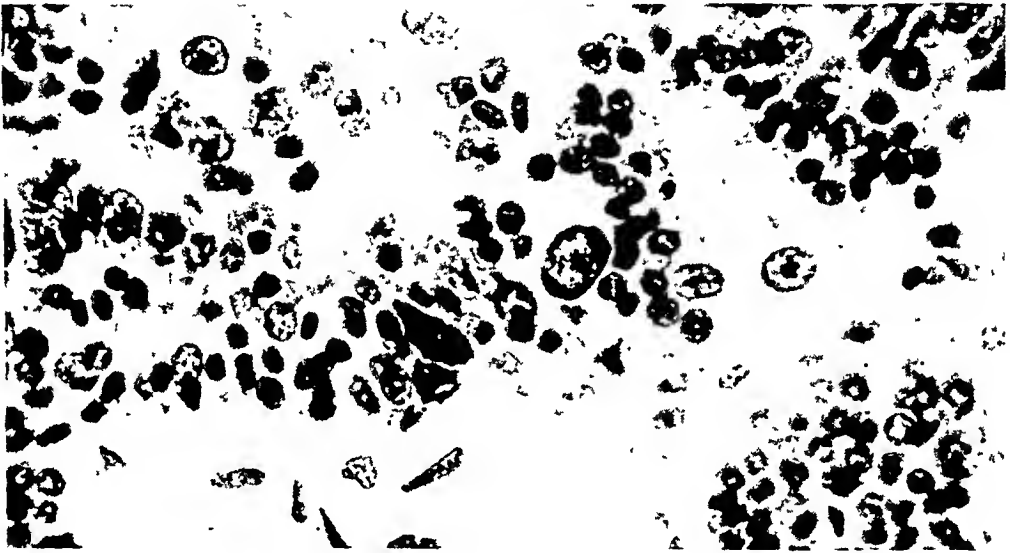


FIG. 3. Case 1.—Variation in size and shape of carcinoid cells in rectovesical tissues. Hematoxylin and eosin. (X1200.)

necrosis. The right kidney had two small nodules of white tissue with some hemorrhagic areas in each pole. The thyroid gland showed multiple small nodules up to 2 cm. in diameter, one of which was hemorrhagic. There were two large nodes adjacent to the head of the pancreas, and a third at the hilum of the liver. Section disclosed homogeneous pink firm tissue in all of these nodes.

*Microscopic description.* All tissues were fixed in formalin and stained with hematoxylin and eosin.

*Rectum and Rectovesical tissues.* There was a massive invasion of these tissues by cords and islands of tumor cells so that neoplastic tissue was predominant. The rectal mucosa was intact but raised by tumor. The typical tumor pattern present throughout these areas corresponded to that which Stout<sup>7</sup> has so aptly described as "festooning ribbons of columnar cells" (Fig. 1). The ribbons were composed of narrow strands of tumor cells, a few cells wide, whose long axes were perpendicular to the long axis of the ribbon. These cells contained round or oval nuclei of uniform size, each of which was about 2 to 3 times the diameter of a lymphocyte. The nuclei contained a diffuse chromatin stippling and no mitoses were seen. The cytoplasm of the cells was well demarcated only at the margins of the ribbons and intercellular boundaries could not be made out. A few cells showed small vacuoles in the cytoplasm. Some groups of cuboidal or columnar cells with

small round nuclei were invading muscle planes. Occasionally a clump or medullary mass of polygonal cells, similar to those usually present in appendiceal carcinoids, were seen. Perineural lymphatic invasion was observed in some areas (Fig. 2). Blood vessel invasion was not seen. About one-half of the tumor, especially that near the serosal surfaces, differed somewhat from that previously described. Resemblance to the festooning ribbons was present but the ribbons were wider and less distinct, the pattern was somewhat labyrinthine, and the cytoplasm stained deeper with eosin. Some variation in size and shape of the nuclei occurred and occasionally nuclei four to five times the usual size were seen (Fig. 3). No prominent nucleoli were present and no mitotic figures were seen. A few tumor giant cells were observed. No definite gland formation was present, although the ribbons of cells gave a pseudo-alveolar configuration in some areas. No glandular secretions nor rosettes were seen. Silver stains had been performed on the first rectal biopsy and the report stated that there was some browning of the cytoplasmic granules of the tumor cells but neither these silver stains nor additional rectal tissue was available to us.

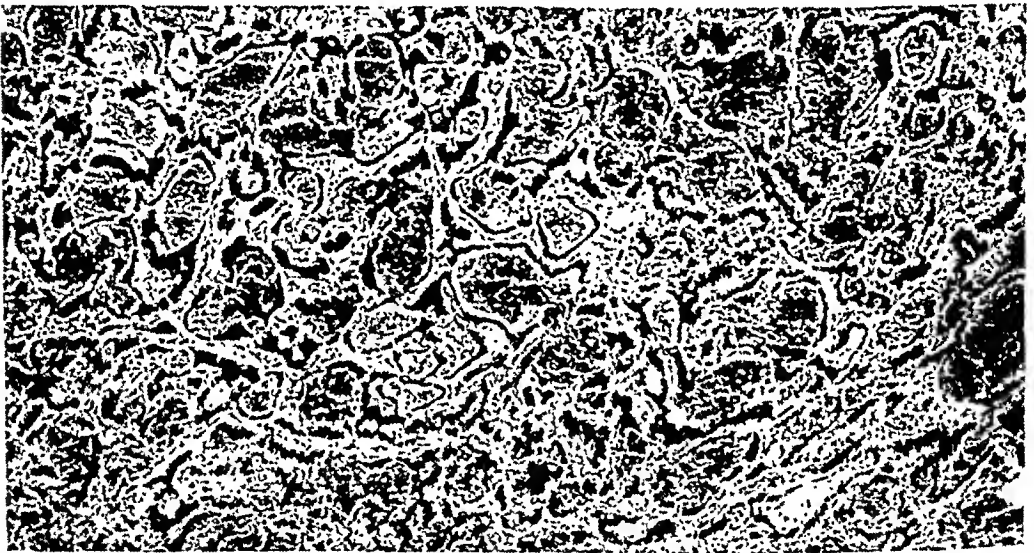


FIG. 4. Case 1.—Blood-filled cysts formed by metastatic carcinoid tumor in the liver. Hematoxylin and eosin. (X150.)

*Liver.* The liver tissue between tumor nodules was essentially normal except for some compression of liver cords. The histologic appearance of the tumor was strikingly different from that described above. Most of the tumor was composed of large blood-filled spaces of varying size (Fig. 4). The walls of these spaces were formed by one or several rows of cuboidal cells, although occasionally broad bands of cells separated the blood-filled spaces. The cells were generally cuboidal with indistinct cell boundaries although columnar cells were occasionally seen. The nuclei were oval to round and had a diffuse finely granular chromatin stippling. Between the cell borders of adjacent blood-filled cystic spaces there was usually a septum of connective tissue containing strands of collagen and small capillaries. The cystic pattern of the tumor was present in all the liver nodules examined, and in addition there were a few small focal collections of cells containing hyperchromatic atypical nuclei of varying size and shape and some tumor giant cells.

*Kidneys.* Tumor nodules were made up essentially of the characteristic festoons of ribbons of columnar cells although some blood-filled cystic areas, similar to those seen in the liver, were observed.

*Lymph nodes.* Tumor cells in the regional, mesenteric and peripancreatic lymph

nodes were composed for the most part of coils of ribbons similar to those seen in the rectum.

*Thyroid.* The tumor in the thyroid gland was composed of blood-filled cystic spaces lined with small cuboidal cells and similar to those seen in the liver.

*Final anatomic diagnoses.* Primary malignant carcinoid tumor of the rectum with invasion of the rectal wall, the rectovesical septum and perirectal nodes, metastases to the liver (massive), right kidney, thyroid, and to the peripancreatic and portal hilar nodes; ascites; emaciation; icterus.

**Case 2.** L.A., a 45-year-old white Italian housewife, entered the Boston City Hospital on Dec. 23, 1946 complaining of nausea, vomiting and marked constipation for one month prior to admission. This was the fourth similar episode within the previous year. No diarrhea or tarry stools were noted. Upon admission the only positive physical finding was tenderness in the epigastrium. Rectal examination at this time was considered to be negative except for some small external hemorrhoidal tabs. Laboratory examinations revealed normal blood and urine. A barium enema examination revealed no intrinsic gastro-intestinal abnormalities. At this time a somewhat enlarged liver was noted, and it displaced the hepatic flexure of the colon medially. The patient was discharged to the surgical outpatient clinic.

Readmission to the hospital three weeks later because of aggravation of previous complaints revealed upon digital rectal examination an annular mass, which just barely admitted the tip of the examining finger, 14 centimeters from the anal sphincter. A sigmoidoscope examination at this time showed an annular constricting lesion with the predominant mass on the posterior wall. The mass was hyperemic and bled easily upon touch, but there were no mucosal ulcerations. Two portions of the lesion were biopsied for histologic examination.

Following a report of the lesion as a carcinoid tumor of the rectum, abdominal exploration was performed. A firm fixed mass was palpable at the terminal rectum below the pelvic peritoneum. The liver and right para-aortic and pararenal areas were studded with large, firm, white tumor nodules. A terminal loop colostomy was performed and the patient's recovery was uneventful. Three weeks later she was discharged to her home. Social Service followup at her home six months later reported that she was having persistent nausea and vomiting and passing large amounts of blood per rectum. She was persuaded to reenter the hospital, but left a short time later, against advice, before any further examinations could be conducted. All subsequent attempts at further treatment were refused.

*Pathologic report:* (M.I.P.—S-47-284). The specimen was received in Zenker's solution and consisted of two small pieces of tissue, somewhat friable, with the larger measuring 1.5 x 0.4 cm.

*Histological descriptions.* Phloxine-methylene blue stain. In some areas the rectal mucosa was intact and normal. In others it was ulcerated and replaced by tumor cells. Throughout the entire rectal wall were masses, strands and columns of cells which had almost completely replaced the muscularis. There was a considerable amount of fibrous tissue accompanying the tumor cells, and foci of fibrin, polymorphonuclear leukocytes, lymphocytes and plasma cells were present throughout the rectal wall. The tumor cells did not show the characteristic festooning pattern of ribbons of cells but occurred in clumps, masses, or columns of round cells with fairly distinct cytoplasmic boundaries. In places the tumor cells had the appearance of a syncytial mass containing many nuclei and indistinct cell borders. The nuclei were round or oval and showed a diffuse chromatin stippling. There was a moderate variation in size and shape of the nuclei and some of them had prominent nucleoli. No mitoses were seen. The cytoplasm of the cells stained heavily with phloxine. No acinar arrangement was present. Connective tissue stains showed an abundant amount of fibrous tissue stroma. The tumor cells resembled those seen in the carcinoid tumors of the appendix but also showed some atypical features such



as the variation in the size of the nuclei, and the presence of some prominent nucleoli. They lacked the festoons of ribbons arrangement seen in many rectal carcinoids. A modification of Bodian's protargol stain<sup>19</sup> revealed that granules in the cytoplasm of the Kultschitzky cells of the rectal glands stained black. Some connective tissue cells in the stroma between the glands also contained silver positive granules but in no cells, recognized definitely as tumor cells, could argentaffin granules be seen. Masson's technique for demonstration of argentaffin granules<sup>2</sup> was attempted on tissue fixed in Zenker's fluid and later "dezenkerized." No argentaffin granules were seen in the tumor cells although some were present in the cytoplasm of the Kultschitzky cells.

Case 3. P.J., a 69-year-old white male entered the Boston City Hospital on April 15, 1947 stating that he had had black stools for one week prior to admission. A similar episode had occurred six weeks previously. During the week prior to admission the patient experienced anorexia and weakness. Physical and laboratory examinations were

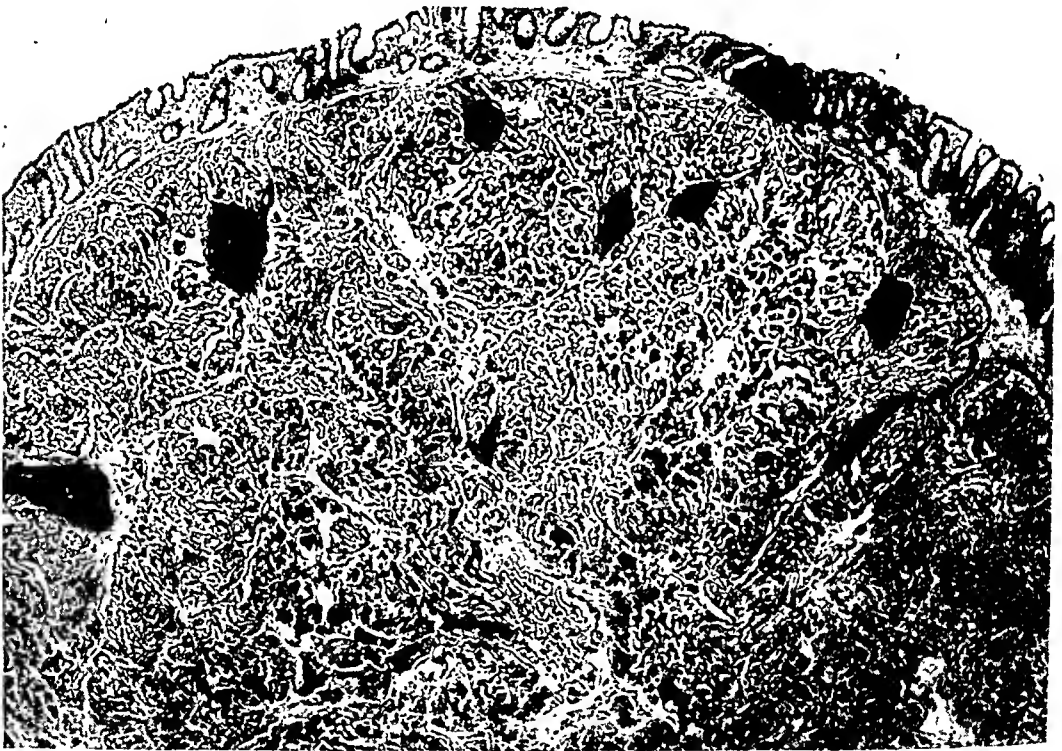


FIG. 5. Case 3.—Submucosal carcinoid tumor showing intact rectal mucosa. Phloxine-methylene blue. (X50.)

essentially negative. Sigmoidoscopy revealed a small polyp about 1.5 cm. wide and 2 cm. long with a small pedunculated base. It was located in the left and anterior walls of the upper portion of the rectum or at the recto-sigmoid junction. The polyp was removed for histologic analysis. A barium enema revealed diverticulosis but no evidence of other lesions.

*Pathologic report.* (M.I.P.—S-47-2445). The specimen consisted of five small fragments of tissue, received in Zenker's solution, the largest measuring 0.8 cm. in diameter.

*Histologic description.* Phloxine-methylene blue stain. The sections are those of a small rectal polyp covered with intact normal mucosa. Replacing almost the entire stalk of the polyp were typical festoons of ribbons of tumor cells (Fig. 5). The ribbons were narrow and averaged two to four nuclei in width. These nuclei were round or triangular in shape and contained a diffuse distribution of nuclear chromatin and no prominent

nucleoli nor mitotic figures. Occasionally nuclei two to three times the average size were seen. Cytoplasmic boundaries were distinct only at the margins of the ribbons. Also present in the sections were small foci of round, uniform-sized cells similar to those seen in the typical appendiceal carcinoid tumor (Fig. 6). Thin strands of fibrous connective

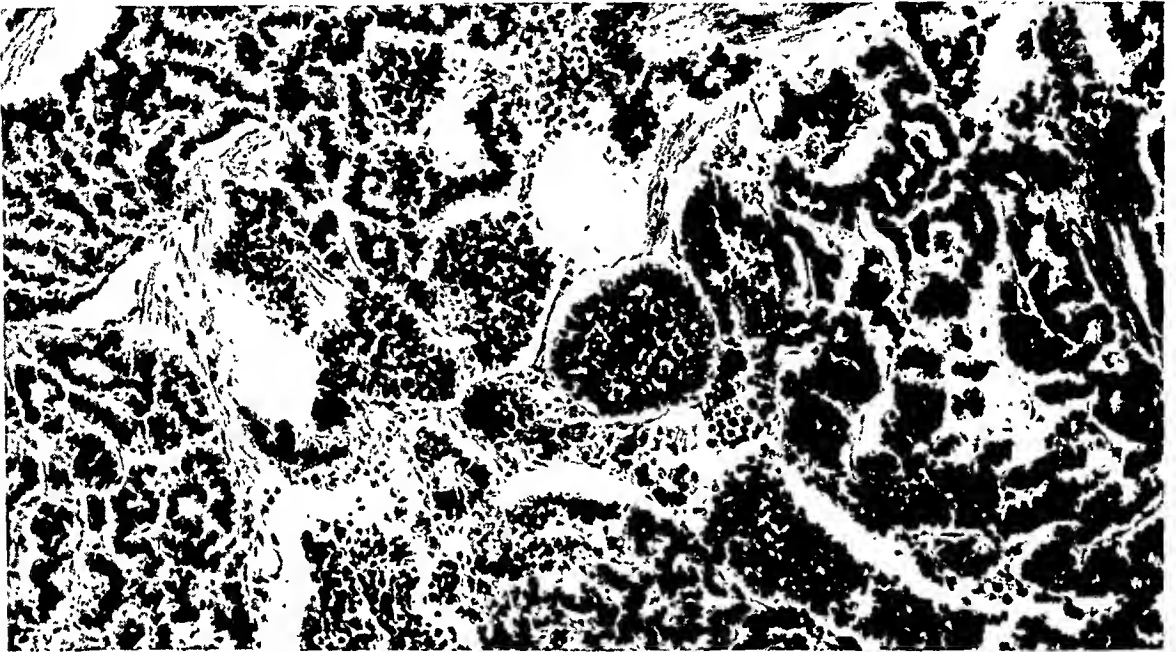


FIG. 6. Case 3.—Submucosal rectal nodule showing characteristic festoons of ribbons arrangement and also nests of carcinoid cells. Phloxine-methylene blue. (X300.)

tissue formed a loose supporting network for the polyp. Scattered throughout the tumor were foci of lymphocytes. No perineural lymphatic or blood vessel invasion was found. The specimen was considered inadequate as far as determining the extent of the invasion and further material was requested. To date this has been unobtainable. Bodian's protargol stain revealed black granules in the cytoplasm of the Kultschitzky cells of the rectal glands and in the cytoplasm of several cells in the interstitial tissue of the mucosa and in the stroma of the tumor. No granules could be seen in cells that were definitely identified as tumor cells. Masson's technic<sup>2</sup> on the tissue fixed in Zenker's fluid showed granules in the cytoplasm of the Kultschitzky cells but not in cells definitely identified as tumor cells.

#### DISCUSSION

Since the studies of Oberndorfer<sup>6</sup> the term "carcinoid" had been used to designate these tumors of the intestinal tract that resemble carcinoma superficially and yet were believed to be benign because of their innocuous appearance histologically and their lack of distant metastases. The work of Masson culminated in his belief that these tumors were derived from the argentaffin (Kultschitzky) cells of the gastro-intestinal tract, and since then many authors have used his designation "argentaffin tumors".<sup>2</sup> We prefer the term carcinoid or carcinoid tumor because our tumors have not shown argentaffin properties. We admit the term is not ideal as the tumor's frequent malignant behavior belies its implied benignity. However, the difference in histologic appearance and clinical course warrant the use of the distinctive term "carcinoid" to separate it from the usual adenocarcinoma of the gastro-intestinal tract.

Carcinoid tumors of the gastro-intestinal tract occur about equally in both

sexes, and at all ages, but in general are most prevalent after the age of 40 years. The most common site of occurrence of these tumors is the appendix. Dockerty, et. al.,<sup>20</sup> state that 0.5 per cent of all appendices removed surgically show argentaffin or carcinoid tumors. Involvement of the ileum, the next most frequent primary site, is said by these authors to occur only a tenth as frequently as in the appendix. In general, the incidence of carcinoid tumors is low, and Ariel found<sup>4</sup> that in a series of 2,373 neoplasms of the entire gastro-intestinal tract, taken from both surgical and autopsy material, only 1.3 per cent were carcinoids.

The distribution throughout the gastro-intestinal tract of carcinoid tumors showing metastases varies somewhat from the overall distribution of both benign and malignant carcinoid tumors. In a series of 68 metastasizing carcinoid tumors of the gastro-intestinal tract collected from the literature by Miller and Herrmann,<sup>21</sup> the primary site of the tumor was the small bowel in 50 of the cases, the appendix in only 14, the colon in 3, and the stomach in one. The incidence of metastases has varied in large series. One author reported as low as 18 per cent,<sup>3</sup> whereas in a recent survey Ritchie and Stafford<sup>5</sup> found that of 332 cases of carcinoid tumor reported in the literature up to 1944, 126 (37.9 per cent) have shown metastases. Dockerty and Ashburn<sup>22</sup> state that carcinoids of the small intestine constitute 23 per cent of all malignant neoplasms in this region. Apparently, the few tumors found in the colon are associated with a high incidence of metastases as Wyatt<sup>23</sup> found that three of nine carcinoids of the colon showed metastases.

Rigdon and Fletcher reviewed the literature<sup>8</sup> on carcinoid tumors of the rectum up to 1946 and found 14 cases. We have found an additional reported case of a rectal carcinoid tumor.<sup>17</sup> More recently, Ehrlich and Hunter<sup>9</sup> have added ten more cases discovered in members of the Armed Forces of World War II. These occurred in males from 18 to 39 years of age and were reported in a series of 813 tumors of the gastro-intestinal tract. From the Mayo Clinic Jackman<sup>10</sup> reported four carcinoid tumors in a series of 87 consecutive patients with submucosal rectal nodules. Of this total of 29 carcinoid tumors of the rectum that have been reported in the literature, two have shown metastases. One of these, Koch's case,<sup>13</sup> showed invasion of the regional nodes, pelvis, bladder, ureters, and metastases to the liver. Siburg's case<sup>16</sup> showed local invasion of the rectal wall and metastases to the regional, sacral, and para-aortic nodes, the liver, and to the thoracic and lumbar vertebral marrow. Our case I showed invasion of the rectal wall, the rectovesical septum and adjacent nodes, and metastases to the liver (massive), right kidney, thyroid, and peripancreatic and periportal lymph nodes. Case II showed involvement of the nodes adjacent to the rectum and metastases to the liver, right pararenal area and para-aortic lymph nodes. Thus of a total of 32 cases four (12.5 per cent) have shown metastases.

The spread of the tumor is usually through the bowel wall to the regional nodes, thence to the liver and occasionally elsewhere. However, blood-borne

TABLE I

Case No.	Author	Year	Sex	Color	Age	Symptoms	Rectal Lesion	REMARKS
1	Stalckow	1912	F		28	None	Submucosal white nodule, 5 mm. diameter, 4 mm. thick, anterior wall, 5 cm. above anus.	
2	Reichel	1924	M		35	None	Pea-sized nodule, 10 cm. above anus, normal mucosa.	
3	Siburg	1929	M		71	Left rib pain, cyanosis, yellow sclerae, swelling of legs, abdomen, scrotum.	Pea-sized nodule, anterior wall, 4 cm. above anus.	Metastasis to regional, sacral, para-aortic node, liver, thoracic, lumbar, vertebral marrow.
4	Brunschwig	1933	M		63	None	Submucosal nodule, loosely adherent, 0.5 cm. diameter, 8 cm. above mucocutaneous junction.	Found incidental to physical examination
5	Humphreys	1934	M		28		Polyp, 0.7 cm. diameter, 5 cm. above anus.	
6	Koch	1940	M		64	Constipation, diarrhea—1 month, tenesmus.	Two-three cm. from anus an infiltrating lesion narrowing 10 cm. of rectum to lead pencil size.	Metastasis to regional nodes, pelvis, bladder, ureters, liver
7 8	Mallory Stout	1940						
	Case I	1942	F	C	19	Bleeding from rectum, constipation — 1 year.	Round, polypoid mass, 18 x 17 x 15 mm., movable, intact mucosa, anterior wall, lower rectal segment, 5 cm. from anus, yellow-white.	Adenomatous polyp removed from adjacent area. Nine year survival, no recurrence
9	Case II		F	C	41	Diarrhea, L.L.Q. pain—5 days, then constipation, anorexia, pain, weight loss—4 months.	Sessile tumor 7 x 4 mm., covered with mucosa, left anterior wall 5 cm. from mucocutaneous junction.	Ileocolostomy for regional ileitis 6 months later. Alive 2 years later
10	Case III		F	C	34	Soreness, protrusion after stools — 4 years. Recent rectal bleeding.	Firm sessile yellow-gray nodule, 11 x 8 mm., with some attached mucosa, anterior wall, 5 cm. above anus.	Hemorrhoids present

TABLE I (Continued)

Case No.	Author	Year	Sex	Color	Age	Symptoms	Rectal Lesion	REMARKS
11	Case IV		F	W	38	Rectal bleeding—2 days.	Firm nodule, covered with mucosa, 7 x 6 x 4 mm., anterior wall rectal ampulla.	Hemorrhoids present. Patient alive, no recurrences 2½ years later
12	Case V		F	W	42	None	Firm, oval plaque, 7 mm. in diameter, anterior rectal wall.	Incidental finding
13	Case VI		M	C	43	None	Elevated, yellow, movable, flattened firm nodule in mucosa and submucosa just above anus.	Incidental finding. Leiomyosarcoma of stomach also present
14	Yaker	1944	M		29	Difficulty in bowel movement, with obstructing sensation in rectum—few weeks.	Sessile, slightly raised, movable, red-brown nodule covered with mucosa, 1.3 x 1.2 x 1.0 mm., anterior wall, 4 inches above anus.	
15	Rigdon and Fletcher	1946	M	C	60	None	Innumerable, rubbery, movable, gray-white submucosal nodules from few mm. to 1.0cm.	Incidental finding
16-25	Ehrlich and Hunter	1947	M		18-38			No malignant, nor metastatic lesions
26-30-32	Jackman Authors Case I	1947 1948	M	W	51	Tarry stools, decreasing calibre—4 months. Weakness, fatigue, weight loss—2 months.	Yellow surface (2 cases).  Three hard yellow nodules, intact mucosa, posterior and left lateral lower rectum, 5 x 3 x 2 mm., 2 x 2 x 2 mm. and 3 x 2 x 1.2 mm. Nodule, 1 cm., 2 cm. above Hilton's line.	Locally invasive (2 cases)
	Case II		F	W	45	Nausea, vomiting, marked constipation—4 episodes in prior year. Later, rectal bleeding.	Annular constricting mass, intact mucosa, prominent on posterior wall. Firm, fixed yellow-brown mass, 1.5 x 0.4 cm. at terminal rectum.	Metastasis to regional and distant nodes, liver, thyroid, kidney
	Case III		M	W	69	Tarry stools—6 weeks and 1 week prior to entry.	Polyp with pedunculated base, 2 cm. long, 1.5 cm. diameter, yellow-brown, left and anterior walls of upper rectum.	Metastasis to regional and distant nodes, liver, and kidney

metastases have been reported in such organs as the spleen, dura, uterus, and ovary. We have seen a carcinoid tumor of the ileum which metastasized to the liver, spleen, pancreas, adrenals, ovary, heart and vertebral marrow. The metastases grossly usually resemble the primary tumor, being various combinations of yellow and white. The metastases in our Case I presented many cystic and hemorrhagic areas similar to the hemorrhagic liver metastases described by Ritchie and Stafford<sup>5</sup> and Gold and Grayzell.<sup>24</sup>

Of particular interest in carcinoid tumors of the rectum has been the lack of reduction of silver salts by these tumors. This reduction and the subsequent demonstration of black granules in the cytoplasm of tumor cells is characteristic of carcinoid tumors arising elsewhere in the gastro-intestinal tract. Stout noted that three otherwise typical carcinoids of the rectum did not reduce silver salts and one gave only a slight browning of the granules present. He postulated that the explanation for the lack of reduction was due to the absence of an enzyme, enteromin, which was necessary for the reaction. As previously mentioned, we were unable to demonstrate granules which reduced silver salts in the cytoplasm of the tumor cells in our cases.

Because of the wide distribution of argentaffin cells throughout the gastro-intestinal tract the multicentric origin of these tumors is possible. Dockerty, et al.,<sup>20</sup> stated that one-third of their cases showed multiple foci of tumor throughout the gastro-intestinal tract. Case I showed at autopsy that only the rectum was involved. The original proctoscopic examination showed three separate nodules in the rectal wall. Case II showed an annular constricting lesion in the rectum. Barium enema and exploratory operation demonstrated no other gastro-intestinal lesions. In Case III a barium enema was negative, but obviously the question of other foci cannot be decided at present.

#### CLINICAL DATA

*Age and Sex.* The ages of the patients having a carcinoid tumor of the rectum have varied from 19 to 71 years and all intermediary decades have been represented. About one-half of the patients have been under 40 years. Metastatic lesions have occurred in patients 45, 51, 64, and 71 years. In 18 cases in which the sex of the patient was mentioned, 11 have been males and seven females. Metastatic lesions have occurred in three males and one female.

*Symptoms.* Of a total of 32 cases known to us (including our three cases) there has been no clinical data available in 13 cases. In nine other cases either no symptoms were mentioned or the tumors were findings incidental to physical examination or necropsy. The remaining 10 cases have had symptoms (Table I). Of these, four patients have had evidence of bleeding with tarry stools in two cases and frank bleeding per rectum in the other two. Constipation was associated with rectal bleeding in one of these cases and decreasing caliber of the stool with tarry stools in another. Three patients had either constipation or difficulty in bowel movement with an obstructing sensation in the rectum, but without bleeding. Three of the four patients with metastases showed the general symptoms of weakness, fatigue, weight

loss and other symptoms usually associated with malignant neoplasms. Three patients had associated diseases (regional ileitis in one case and hemorrhoids in two other cases) which obscured the relative importance of the carcinoid tumor in the causation of symptoms. Symptoms had usually been present from a week or two to a few months, although one patient had constipation and rectal bleeding for one year prior to seeking medical attention.

There has been some discrepancy between the extensiveness of the lesions and symptoms. Yaker remarked<sup>18</sup> on the small lesions of the rectum ( $1.3 \times 1.2 \times 1.0$  mm.) in his case and yet the patient complained of some difficulty with bowel movements and of having an obstructing sensation in his rectum. However, Rigdon and Fletcher stated<sup>8</sup> that in their case the lesions were so numerous that one could not touch the rectal wall without touching tumor, yet, the rectal lesions were incidental findings at necropsy.

*Physical Findings and Gross Appearance of the Tumor.* In 14 cases in which the quadrant of localization in the rectum was mentioned, eight showed the lesion on the anterior wall, two on the left anterior wall, and two were described as diffusely infiltrating the rectum. One case had innumerable nodules present throughout the rectum and one of our patients showed lesions in both the anterior and posterior walls.

The type of lesions have been mentioned in 18 cases. A solitary nodule was present in 14 cases, multiple nodules in two, and annular constriction lesions in two other patients. In 10 cases in which the distance of the tumor above the anus was mentioned, five were 5 cm. above, two 4 cm., one 10 cms., one 8 cm., and one 2 to 3 cm. from the anal sphincter. Of 15 discrete solitary tumors nine were reported to be nodular, three polypoid, two sessile, and one was called a plaque. In 16 cases in which the lesion was described, 12 of them were noted to be either partly covered with mucosa or entirely submucosal. The solitary lesions ranged in size from 0.2 cm. to 1.8 cm. in diameter and averaged about 1 cm. in 13 cases. Cut surface of the lesion was mentioned in 10 cases; in seven of these a yellow color was either predominant or noteworthy, two were white and one was red-brown. Five lesions were described as freely movable.

*Differential Diagnosis.* Carcinoid tumors diffusely infiltrating the wall of the rectum cannot be clinically differentiated from an infiltrating carcinoma of the rectum. In one case such a lesion in a female patient raised a question of lymphopathia venereum. The polypoid type of carcinoid resembles grossly an adenomatous polyp or a polypoid type of adenocarcinoma. Sessile or plaque-like lesions may occur in either carcinoma or carcinoid. As previously mentioned, the majority of carcinoid tumors of the rectum have some intact mucosa covering them or are submucosal; however, a similar finding may occur in adenocarcinoma. Furthermore, the nodular carcinoid, although the most frequent in type, makes up only a small percentage of rectal submucosal nodules. Jackman<sup>10</sup> has reported on 87 such lesions and only four were carcinoid tumors. Previous injection therapy, inflammatory lesions, benign con-

nective tissue tumors, and rarely malignant lymphomas, accounted for the other submucosal lesions.

It is obvious that only by histologic examination can a diagnosis be made with any degree of assurance. Even with pathologic examination there is the possibility that these lesions might be mistaken for adenocarcinoma of the rectum as has occurred in some instances in the past. The recent report of 10 cases in relatively young members of the Armed Forces<sup>9</sup> suggest that the lesion is more frequent than previously realized.

*Treatment.* Most authors state that the plan of choice in treating malignant carcinoid tumors of the gastro-intestinal tract is resection of the primary site and as much of the metastatic lesions as is feasible. It is well known that, as a rule, the tumor is slowly growing and patients with known metastases have lived for many years. In one recorded case<sup>25</sup> it has been stated that following resection of a primary carcinoid tumor of the small bowel, mesenteric metastases were noted but not removed. At necropsy 20 years later the same metastases were observed and except for some calcification were apparently unchanged.

In carcinoid tumors of the rectum the problem is somewhat complicated. Only four cases out of a total of 32 known to us have been associated with metastases. Local excision of the lesion has been followed in two cases in which a solitary rectal polyp was found, by survival periods of 9 and 2½ years without any evidence of local recurrence or metastases, and a third patient was known to be alive two years after removal of a small rectal carcinoid.<sup>7</sup> The fact that the lesions occur often in relatively young patients and that extensive surgery in the rectum carries with it considerable discomfort and annoyances associated with colostomy, is a factor to be weighed against the apparent low grade malignant nature of the neoplasm.

From our limited experience of only three cases we can no more than point out what appear to be salient features. Our Case 1 died with generalized metastases two years after the onset of his symptoms. Case 2 had liver, kidney and lymph node involvement and was severely debilitated when last seen about two years after the onset of her symptoms. It is very difficult to differentiate, on histologic appearance, those lesions that have been associated with metastases and those that have not been, although two of our cases with metastases showed areas of atypical cells (Fig. 3). If, on rectal examination, an infiltrating type of lesion is found, a malignant type of lesion is implied but this is not infallible. Infiltrating and annular constricting lesions have been associated with metastases in two cases, but liver, bone marrow, and lymph node metastases were present in a case showing only a solitary, pea-size rectal lesion.<sup>16</sup> In one case showing almost complete involvement of the rectal wall with innumerable nodules, autopsy revealed no metastases.<sup>8</sup> The age of the patient may be significant, for the nine-year survival after local excision was in a 19-year-old girl and the ages of the patients showing metastases were 45, 51, 64, and 71 years. However, at least two cases of malignant carcinoid



tumors of the small intestine have occurred in patients under 40 years of age<sup>26</sup> so that the age *per se* may not be too significant.

It would appear that solitary freely movable lesions in young patients might be excised locally and the patient carefully followed for signs of local recurrence or metastases. Annular constricting or diffusely infiltrating lesions in middle-aged or elderly patients would appear to call for extensive surgery such as that used in adenocarcinoma of the rectum. Cases lying between these two extremes call for considerable clinical judgment and pathologic acuity, and definitive lines of therapy probably will be drawn only after a large number of cases has been properly assayed.

The application of radiation therapy to carcinoid tumors of the rectum or their metastases has not been reported, to our knowledge. Several authors,<sup>4, 27, 28</sup> have observed that metastases from carcinoid tumors arising elsewhere in the gastro-intestinal tract appear to respond well to irradiation if the primary tumor is removed. These reports suggest that some carcinoids and their metastatic lesions may be radiosensitive.

#### SUMMARY

Three cases of carcinoid tumor of the rectum have been reported. One patient showed at necropsy metastases to the liver, kidney, thyroid and distant lymph nodes. In the second patient abdominal exploration revealed metastases to the liver, kidney region, and distant nodes. In the third patient only a small polyp was found in the recto-sigmoid area.

Thirty-two cases of carcinoid tumor of the rectum have been reported (including our three). Of these, four (including our two) have been associated with distant metastases.

The pertinent literature is reviewed, the symptoms and signs summarized, and the differential diagnosis, pathology and treatment of these neoplasms briefly discussed.

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SINCE SUBMISSION OF THIS REPORT THE AUTHORS HAVE HAD AN OPPORTUNITY TO REVIEW 5 MORE RECTAL CARCINOID TUMORS, IN 2 OF WHICH THERE WAS AT LEAST INVASION OF THE RECTAL WALL AND ADJACENT TISSUES. IN ADDITION, WE HAVE NOTED A REFERENCE BY DUKES\* TO 9 CASES OF CARCINOID TUMOR OF THE ANO-RECTAL REGION SEEN BY HIM IN A STUDY OF 203 CARCINOMAS OF THAT AREA. THREE OF THE CARCINOIDS WERE DISCOVERED IN SURGICAL SPECIMENS CONTAINING CARCINOMA OF THE RECTUM. IN ONLY ONE CASE WAS ADEQUATE FOLLOW-UP AVAILABLE: THE PATIENT WAS A 34-YEAR-OLD WOMAN WHO WAS WELL AND FREE OF RECURRENCE 9 YEARS AFTER LOCAL EXCISION OF THE LESION.

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# MORBIDITY AND MORTALITY IN TALC GRANULOMA: REPORT OF A FATAL CASE \* †

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DESPITE THE RAPIDLY INCREASING NUMBER of reports of postoperative complications and morbidity in which talcum powder has been incriminated as the etiologic factor, this noxious agent continues in use. The purpose of this paper is to re-emphasize the incidence of morbidity due to this complication and report a case in which talc granuloma not only necessitated an unprecedented number of laparotomies but ultimately caused the death of the patient.

## INCIDENCE AND MORBIDITY

When Antopol<sup>1</sup> in 1933 described the first case of intraperitoneal granuloma due to talc, he started a trend of thought which has since been developed and reported upon by many investigators. Antopol, as others before him, was primarily interested in lycopodium spores as a pathogenic factor in the production of tubercle-like granulomatous lesions. Indicative of the frequency and morbidity are the numerous clinical reports which have appeared in the literature since 1933. Most notable are those of Feinberg<sup>2</sup>, Owen<sup>3</sup>, Ramsey and Douglass,<sup>4</sup> McCormick and Ramsey,<sup>5</sup> Byron and Welch,<sup>6</sup> Ramsey,<sup>7</sup> and German,<sup>8</sup> in which two to five laparotomies were necessitated for the relief of obstruction due to talc granuloma. German<sup>8</sup> reported one case in which five previous laparotomies had been performed. Lichtman Et Al<sup>9</sup> reported talc crystals with surrounding foreign body response in 21 of 100 consecutive surgical cases in which there were dense adhesions resulting from multiple previous operations.

In addition to intraperitoneal granulomas due to talc, Antopol and Robbins,<sup>10</sup> Erb,<sup>11</sup> Antopol,<sup>1</sup> Cline,<sup>12</sup> Fienberg,<sup>2</sup> Ramsey and Douglass,<sup>4</sup> and Lichtman Et Al,<sup>9</sup>X have reported identical lesions in the skin, vagina, rectum, eye, gallbladder, healing surgical wounds, and brain. Lichtman reported granulomas developing in scars from two months to 36 years after talc was implanted in the skin. In the Veterans Hospital, Wood, Wisconsin, Ross<sup>13</sup> has found a large number of granulomatous lesions of the foreign body type among the routine surgical specimens. Of these most were definitely identifiable as talc granulomas. This does not take into account the many draining sinuses occurring in operative wounds which were not biopsied and examined for talc crystals.

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#### EXPERIMENTAL PRODUCTION OF LESIONS

Miller and Sayers,<sup>14, 15, 16</sup> reporting on an excellent series of experiments with various dusts in 1933 and 1934 pointed out that the peritoneal response to foreign bodies falls into one of three types e.g.: (1) absorptive, in which the foreign material is absorbed and no permanent lesion is formed; (2) proliferative, in which there is tubercle formation and proliferation of fibrous tissue (talcum falls into this class); (3) inert, in which the foreign material remains in the peritoneal cavity but produces no reaction at all. Owen<sup>3</sup> in 1936 produced talc granulomas experimentally in the peritoneal tissue of rabbits which were grossly and histologically identical to those removed from the peritoneum of a young woman two years after appendectomy. Bethune<sup>17</sup> in 1935 demonstrated the effectiveness of commercial talcum powder in producing pleural adhesions in preparation for lobectomy. Lichtman Et Al,<sup>9</sup> and Lee and Lehman,<sup>18</sup> in well-controlled experiments on dogs, have conclusively demonstrated the ability of talc to produce dense adhesions in the peritoneal cavity, and to cause and perpetuate both external and internal fecal fistulas.

#### COMPOSITION AND PORTALS OF ENTRY

Kroneberg<sup>18</sup> found the composition of ordinary commercial talc used on surgical gloves to be talc 82.7%, calcium carbonate 8.7%, magnesium carbonate 7.6%, 55% of the particles being less than 5 microns in diameter. Weed and Groves,<sup>20</sup> in observations on 4,569 operations at the Central Surgery of the Indiana University Medical Center, showed that perforations of gloves occurred in 22.6% of all gloves used, thus providing a portal of entry for talc crystals. Our own observation reveals an additional portal in that rubber drains are liberally powdered with talc for autoclaving. The impossibility of completely removing all talc crystals from rubber drains or gloves is easily demonstrated. Regardless of how thoroughly they are washed, subsequent examination under the polarizing microscope will reveal many birefringent crystals still clinging to the rubber.

Although much has been written of complications and morbidity due to talc granulomas, we were unable to find any report in which death was ascribable to this lesion and, consequently, no records of autopsy findings in human material. As previously stated, the largest number of multiple operations was the five reported by German.<sup>8</sup> In the case herein presented fifteen operations were performed, death ultimately ensued, and an autopsy was done. It should be stated that this patient was operated upon initially while in the Army and only the last two surgical procedures were carried out in the Veterans Hospital at Wood, Wisconsin.

#### REPORT OF A CASE \*

A.L.M., VA-93462, had no serious illness prior to 1942 when her present illness actually began.

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\* This case is published with the permission of Dr. Forrester Raine, Senior Consultant in Surgery, who was the operating surgeon.

*History and Clinical Course.* In December of 1942, at the age of 36, the patient had her initial operation for intestinal obstruction. At surgery an adenocarcinoma of the descending colon was found. The tumor together with 10 cm. of colon was removed and a primary end-to-end anastomosis was made. On her seventh postoperative day there was a disruption of the wound which required secondary closure. A draining sinus persisted in the operative wound. Approximately three months after the first operation she became completely obstructed and was again operated upon. At this operation a stricture of the descending colon was found at the site of the previous anastomosis and a Mikulicz type



FIG. 1.—Segment of terminal ileum, removed at surgery, showing numerous granulatous nodules.

resection was done. Pathologic examination of this specimen showed a granulomatous-type lesion with foreign body giant cells and was thought by the pathologists to be due to suture material (this examination was done elsewhere and, unfortunately, the slides could not be obtained for re-examination under the polarizing microscope).

Between her first operation and her final admission to this hospital she was operated upon 14 times for adhesions and intestinal obstruction. Her story was monotonously similar for all these episodes, the sequence being surgery, hyperperistalsis and pain, alternating diarrhea and constipation, complete obstruction with nausea and vomiting, and

finally more surgery. At one of these operations, in February of 1944, a cholecystectomy was done. In June of 1946 an exclusion of the terminal 24 inches of ileum was effected by side-to-side anastomosis with the ascending colon. The terminal 24 inches of ileum which was an inseparably adherent, non-functioning mass was thus by-passed by the fecal current. Following this procedure the patient was able to get along fairly well although discomfited by persistent distention of the right lower abdomen and 12 to 14 loose watery stools daily. During this time she perspired freely, was easily fatigued, had insomnia and



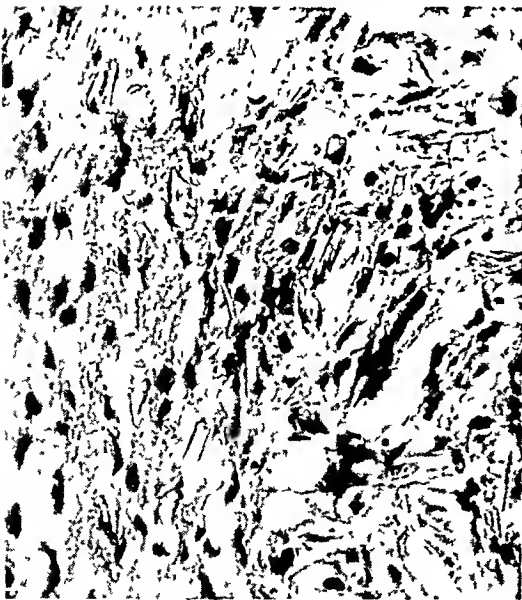
FIG. 2.—Remains of intestinal tract as seen at autopsy. The probe is in the cecal fistula. The entire mesentery and bowel show chronic, granulomatous changes.

had daily swelling of her feet and puffiness of her eyes. She re-entered the hospital in January of 1947 because of severe headache and the persistent diarrhea. In February, 1947 she again became completely obstructed. Conservative treatment was hampered by a severe sensitivity to rubber, and surgical intervention was necessary. At operation the peritoneal cavity was found to be almost completely obliterated on the right side by dense adhesions. Adhesions were freed and the excluded portion of ileum comprising the terminal 24 inches was excised in toto. On the 10th postoperative day the wound disrupted and a fistula developed. All measures directed toward controlling the fistula and maintaining nutritive balance failed and the patient died on the 86th postoperative day.

## SURGICAL SPECIMEN

Pathologic examination of the portion of ileum removed in February of 1947 showed a chronic adhesive peritonitis with small greyish-white nodules scattered over the serosal surface (Fig. 1).

A



B



C

- FIG. 3A.—Granuloma on the surface of the right ovary. Hematoxylin and Eosin  $\times 90$ .  
FIG. 3B.—Higher magnification under ordinary light. Talc crystals are visible. Hematoxylin and Eosin  $\times 400$ .  
FIG. 3C.—The same field under polarized light which makes the crystals more clearly visible. Hematoxylin and Eosin  $\times 400$ .

Microscopic examination showed a thickening of the serosa with fibrosis, lymphocytic infiltration, and foreign body giant cells which had engulfed crystalline material. Examination under the polarizing microscope showed this crystalline material to be composed of birefringent crystals which were morphologically identical with talc crystals.

#### AUTOPSY FINDINGS

At autopsy the body presented the typical emaciated appearance of death by starvation. The cause of death was inanition due to chronic adhesive peritonitis. The gross anatomical findings were: (1) ulcerative gangrene

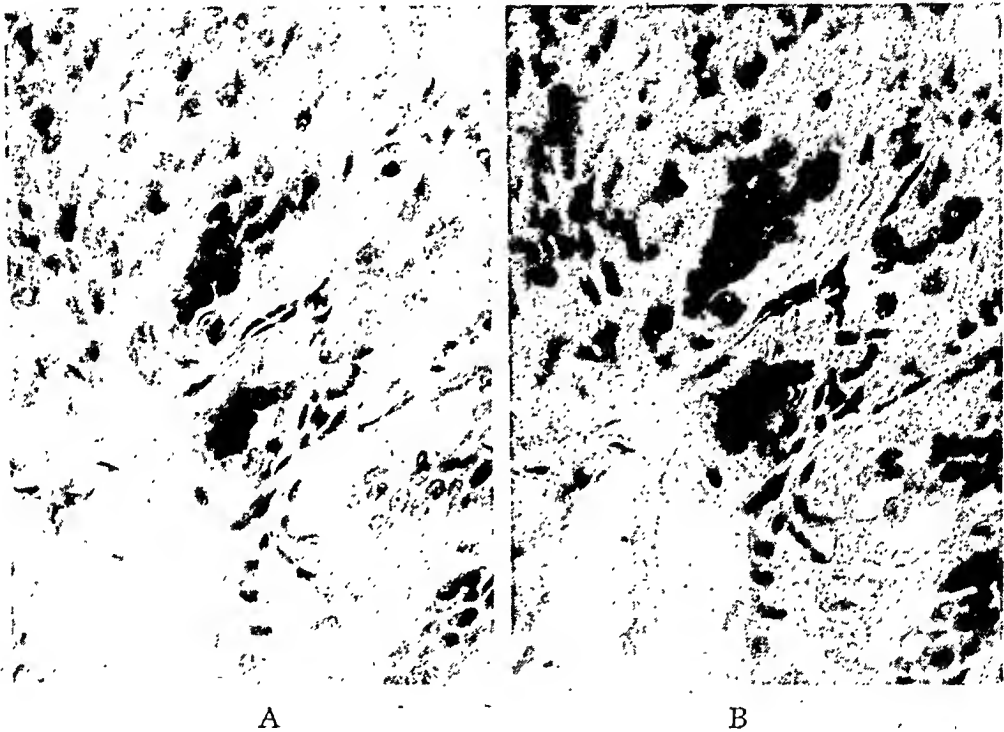


FIG. 4A.—Section of peritoneal nodule (ordinary light) showing typical foreign body granuloma formation with talc crystals and large foreign body giant cells. Hematoxylin and Eosin x 400.

FIG. 4B.—Same field under polarized light to show up crystals more clearly. Hematoxylin and Eosin x 400.

of the cecum with a fistula through the right abdominal wall; (2) intra-abdominal fistulous tract from the cecum to the right pelvis; (3) localized sero-fibrinous peritonitis of the pericecal region and pelvis; (4) diffuse chronic adhesive peritonitis; (5) diffuse talc granulomatosis of the peritoneal surfaces; (6) ulcerative esophagitis.

Only the abdomen merits description in this report. All that remained of the gastro-intestinal tract was the stomach, duodenum, four loops of small bowel, and approximately two-thirds of the large bowel. The omentum and remaining loops of small bowel were firmly adherent to the anterior abdominal wall at the medial edge of the fistulous tract forming a pocket in the right



half of the abdomen containing necrotic and gangrenous cecum and ascending colon. This pocket was connected with a similar pocket in the right half of the pelvis by an intraabdominal fistula from the lower portion of the cecum. The right ovary, Fallopian tube, and uterus were firmly bound to the right pelvic wall by dense adhesions. Scattered throughout the peritoneal surface and in the mesentery of the bowel there were numerous small greyish-white, tubercle-like nodules which varied in diameter from one to five mm. (Fig. 2). Mesenteric lymph nodes were hypertrophic.

#### MICROSCOPIC EXAMINATION

All organs microscopically showed degenerative changes. Sections of the bowel showed gangrene and chronic enteritis. The intestinal wall was thickened by a chronic inflammatory process involving the serosal surface and characterized by lymphocytic infiltration, fibrosis, and foreign body giant cells containing birefringent talc crystals. Mesenteric lymph nodes showed a chronic lymphadenitis without the presence of talc crystals. Kidneys showed a nephrosis and calcinosis manifested by deposits of calcium in the convoluted tubules. Sections through the right ovary showed a chronic granulomatous perioophoritis. Figure 3a is a low power field of a section of the right ovary showing a typical granuloma on the serosal surface with an underlying marked foreign body reaction. Figure 3b is a high power field of the same section showing the marked chronic inflammatory reaction with fibrosis, foreign body giant cells, and talc crystals. Figure 3c shows the same field under polarized light which brings out the crystals more clearly. Sections of the nodules found in the peritoneal surface show a typical foreign body granuloma formation characterized by lymphocytic infiltration, foreign body giant cells containing birefringent talc crystals and early fibrosis (Fig. 4a and 4b).

#### DISCUSSION

This patient was cured of her carcinoma since no evidence of recurrence or metastases was found at autopsy. The 15 subsequent operations were all necessitated by intestinal obstruction due to adhesions which we feel can be directly ascribed to talc granuloma. Both the gross and microscopic appearance of the bowel removed at surgery and the sections taken at autopsy support a diagnosis of talc granuloma. The massive, dense adhesions, the small, greyish-white nodules in the peritoneum, and the formation of uncontrollable fecal fistula are typical of the pathologic changes described by Lichtman,<sup>9</sup> Lee and Lehman,<sup>18</sup> and other investigators in both human and animal material. The finding of large numbers of birefringent crystals surrounded by a foreign body inflammatory reaction is conclusive evidence that talc was the pathogenic agent in the production of this clinical and pathological picture. The occurrence of a chronic lymphadenitis without the finding of talc crystals in the lymph nodes themselves is explained by Lichtman<sup>9</sup> in his description of the pathogenesis of talc granuloma as being due to the fact that talc immobilizes phagocytes without destroying them, so that migration from the original site is limited, thus producing circumscribed granulomas.

The role of infection in the formation of fibrous adhesions and the activation of granulomatous lesions due to talc is debatable. Lichtman,<sup>9</sup> along with German,<sup>8</sup> feels that infection is an important factor whereas Lee and Lehman<sup>18</sup> were able to demonstrate, in dogs at least, that neither trauma nor infection were necessary to the formation of granulomas or adhesions. It is probable that in the case under discussion, both trauma and infection contributed materially to the severity of the reaction. An interesting point for speculation is the fact that this patient was sensitive to rubber, reacting promptly and violently to even a gastric suction tube. This may also have been a factor in the severity of the peritoneal reaction and might be indicative of an unusual sensitivity to other foreign substances.

An additional interesting sidelight in this case was the finding of nephrosis and calcinosis in the microscopic examination of the kidneys. These findings in this particular patient with a long history of intestinal obstruction and vomiting (and with marked shortening of the gastro-intestinal tract) are typical of the changes described by Martz.<sup>21</sup>

Since talcum powder has been so conclusively demonstrated to be a dangerous agent in surgery and one whose deleterious effects in producing postoperative complications, increasing morbidity, and even causing death, far outweigh its advantages, it seems logical that its use should be discontinued. In the past several years numerous investigators have been searching for a suitable substitute for talcum powder. Of these, Seelig et al<sup>22</sup> in 1943 recommended the use of potassium bitartrate which they found would meet the physical requirements of steam sterilization and at the same time was innocuous when placed in the peritoneal cavity. More recently, Lee and Lehman,<sup>18</sup> after a well-controlled series of experiments with several agents, recommended the use of a commercially prepared corn starch derivative which proved to be, in both laboratory experiments and clinical use, a perfectly satisfactory substitute for talcum powder in all respects.

#### SUMMARY AND CONCLUSIONS

1. From a survey of the literature and from our own observations we must conclude that talcum powder is a dangerous agent which has no place in modern surgery. The complications and morbidity which confront the surgeon and the economic loss to the patient, all ascribable to talc, are staggering.
2. In the case herein presented talcum powder was undoubtedly directly responsible for the death of the patient.
3. Of the substitutes offered to date, the modified corn starch preparation recommended by Lee and Lehman seems best to fulfill all the requirements of a dusting powder for use on surgical gloves and drains.

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# AN UNUSUAL COMPLICATION OF A MECKELIAN DIVERTICULUM\*

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THE PERSISTENCE OF THE vitello-intestinal duct in man, in whole or in part, is variously estimated to occur in from 1 to 2 per cent of instances. The early human embryo is imperfectly differentiated from a large and conspicuous yolk sac and communicates with this sac widely by its ventral surface. This communication forms the lumen of the vitelline duct; it is conspicuous during the first month of gestation, but it usually disappears by the sixth or seventh week of fetal life. In cases in which the closure and obliteration of the vitelline (umbilical) duct are imperfectly effected before birth, a portion, or even all of the duct may persist as a pervious tube. The anomaly caused by a persistent vitelline duct is termed "Meckel's diverticulum." The vitelline duct is accompanied in the embryo by the umbilical vessels. The latter, like the duct itself, may persist and in adult life may be found close to the diverticulum; they may have an independent course or they may lie along the free border of the mesentery of the diverticulum.

Eisendrath recorded six conditions which may be found to exist at birth and which are due to the persistence of the vitelline duct and umbilical vessels: (1) a complete canal which opens at the umbilicus and communicates with the lumen of the ileum; (2) a canal which opens at the umbilicus and ends blindly at a variable distance within the abdominal cavity; (3) a persistent intermediate portion of the duct which has no communication externally at the umbilicus or internally with the ileum, but which forms a cystoma owing to retained secretion; (4) a canal which is limited to the proximal end and which opens into the ileum; (5) a cord containing the umbilical vessels which may persist as an independent structure and which may be attached to the umbilicus separately. This vascular cord may take an independent course, the vessels may run along the free border of the mesenterium of the diverticulum or they may run from the diverticulum to form a cord which is commonly known as the terminal ligament: and (6) an absent or rudimentary diverticulum, in which event the only evidence of the presence of a congenital condition is a cord which contains the umbilical vessels, or traces of them and which extends from the mesentery to the umbilicus.

Numerous reports of the occurrence of complications secondary to Meckel's diverticulum are recorded in the literature. These include intestinal obstruction due to intestinal volvulus, hemorrhage due to ulceration of aberrant gastric mucosa in the lumen of the diverticulum, intussusception, perforation.

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neoplastic involvement of the diverticulum, calculus formation in the diverticular pouch and umbilical fecal fistula.

Reports of an external fistula presenting at the umbilicus, owing to Meckel's diverticulum, have been confined to infants or children of a very early age. The development of an external fecal fistula in adult life owing to a patent vitelline duct, with persistent attachment at the umbilicus, we believe to be an uncommon occurrence. We were unable to find any record that such a complication had been previously reported.

We recently had the opportunity of seeing a patient in whom an external fecal fistula, secondary to Meckel's diverticulum, developed late in life. Because of the unusual nature of the case and the difficulties presented in diagnosis we felt it would be worth while to report it.

#### REPORT OF CASE

A 75-year-old widow had always been in good health except for a moderate hypertension of many years' duration. She had undergone cholecystostomy for cholelithiasis 30 years before admission to the clinic and had recovered therefrom without incident. Four days prior to admission, after the patient had played rather strenuously with her young grandson, generalized crampy abdominal pain, followed by vomiting and moderate distention of the abdomen developed. She consulted her family physician, who performed a roentgenologic examination of the stomach and colon and found them normal. She became progressively more ill and was referred to the clinic for an opinion.

At the time of admission the patient was very ill, toxic and dehydrated. The tongue was dry and furred. The blood pressure was 170 mm. of mercury systolic and 106 mm. diastolic. Examination of the chest revealed depression of breath sounds, with fine crepitant râles at the base of the right lung. The abdomen was distended and moderately tympanitic; few peristaltic sounds were audible. About the umbilicus was a red indurated area of cellulitis which measured approximately 3 inches (7.5 cm.) in diameter, with an area of subcutaneous crepitus at its upper edge. The clinical picture was that of ileus with complicating bronchopneumonia. It was difficult to account for the periumbilical cellulitis.

The voided urine contained albumin, grade 2 (on the basis of 1 to 4, in which 1 represents the mildest, and 4 the most severe condition), numerous hyaline and a few granular casts, and a few erythrocytes and leukocytes. The Kline flocculation test of the blood serum was negative. The hemoglobin measured 14.6 Gm. per 100 cc. of whole blood and the leukocytes numbered 6,000 per cubic millimeter. The value for blood urea was 144 mg. per 100 cc. and for the serum chlorides, 544 mg. per 100 cc. A roentgenogram of the chest showed pulmonary congestion and beginning bronchopneumonia on the right side. A roentgenogram of the abdomen revealed some distention of the coils of the small intestine.

Food could not be retained because of nausea, so fluids were given intravenously. Because of the pneumonia, 2.5 Gm. of sodium sulfadiazine were given intravenously every day. The abdominal distention was relieved by intestinal intubation.

Despite every supportive measure available, the patient became progressively more ill. There was persistent fever, with a temperature which varied between 101° and 103° F. (38.3° to 39.4° C.). The pneumonia became more extensive. Necrosis and ulceration developed in the area of periumbilical cellulitis and foul purulent material, with a strongly fecal odor, began to drain from this point on the third hospital day. Death occurred on the sixth hospital day.

At necropsy we found a small opening at the umbilicus from which was oozing thin purulent fluid with a fecal odor. On opening the peritoneal cavity no evidence of

inflammation was noted. A bandlike structure arose from the ileum 15 cm. proximal to the ileocecal valve and extended to an attachment at the umbilicus. This appeared to be a persistent vitello-umbilical duct (Meckel's diverticulum).

There was an abnormal mobility of the cecum and ascending colon, these structures lying in the left half of the abdomen. There was chronic ulcerative cholecystitis with cholelithiasis. The gallbladder contained 150 cc. of purulent fluid and five black stones which averaged from 0.3 to 0.6 cm. in diameter. Thrombosis of the left iliac and femoral veins had led to bilateral pulmonary embolism, and small infarcts of the lung were



FIG. 1.—Connection of the Meckel's diverticulum with the anterior abdominal wall. The diverticulum has been opened longitudinally and the probe is in the fistula. The arrow shows the most distal point of contact of the diverticulum with the ileum.

present. Incidental findings were a traction diverticulum of the esophagus associated with healed tuberculosis of the lungs and hilar lymph nodes, and diverticulosis of the sigmoid. The immediate cause of death was considered to be extensive bronchopneumonia which had involved both lungs.

On closer examination, the Meckel's diverticulum (Fig. 1) was found to arise from the lumen of the ileum at an oblique angle, the proximal 4 cm. of it being incorporated in the wall of the ileum; both the diverticulum and the ileum were covered by a common serosa which, in effect, produced a double lumen tube. The opening into the ileum was approximately 1.3 cm. in its greatest diameter, and the average diameter of the proximal portion of the diverticulum was 0.8 cm. The length of the diverticulum, from its point of contact with the bowel wall to its junction with the anterior abdominal wall at the umbilicus, was 17 cm. The distal portion of the diverticulum, for a distance of 6 cm., ran parallel to the anterior abdominal wall and was covered by parietal peritoneum.

The terminal 2.5 cm. of the diverticulum was gray in appearance and necrotic, but it was intact throughout, except for the tip. A fistulous tract began at the tip of the diverticulum, coursed through the subcutaneous fat and an abscess in the subcutaneous tissue, and opened externally at the midpoint of the umbilicus. The subcutaneous abscess contained approximately 4 cc. of pus. There was no gross evidence of ulceration on the mucosal surface of the diverticulum proximal to its attachment to the anterior abdominal wall.

Microscopic examination of sections taken from the distal portion of the diverticulum showed chronic suppurative inflammatory changes with active proliferation of fibroblasts and capillary loops. Much of the mucous membrane of this portion of the diverticulum was destroyed. The lumen of the diverticulum was filled with polymorphonuclear leukocytes and necrotic debris, and it communicated freely through a necrotic wall with an abscess in the fibrous and adipose tissue of the anterior abdominal wall. Sections taken from the proximal portion of the diverticulum showed a minimal amount of acute inflammatory exudate on the serosal surface; otherwise they were not remarkable. There was no evidence, from any section taken, of generalized peritonitis. A section of the diverticulum at its junction with the anterior abdominal wall confirmed the gross impression that it was covered with peritoneum; this led to the conclusion that the diverticulum was congenitally located in the position in which we found it, and that it had not become secondarily attached as a result of an inflammatory process.

#### COMMENT

Aberrant gastric mucosa is sometimes found in Meckel's diverticulum. Such aberrant tissue has led to ulceration and severe bleeding from the gastrointestinal tract. It is not unreasonable to believe that an ulcer which develops in this way could perforate and could result in an abscess and fistula similar to those noted in our case. A meticulous search of serial blocks of tissue afforded no confirmation whatsoever of this postulate. However, since the mucosa was completely destroyed in some of the sections, that such a possibility was existed in our case cannot be positively excluded. More probably the sequence of events was, as our evidence suggests, inflammation of the diverticulum which led to necrotic diverticulitis with perforation, abscess and ultimately fistula formation. This complication of Meckel's diverticulum in the eighth decade of life is undoubtedly unusual, but that it does occur, again emphasizes the fact that Meckel's diverticulum is a constant hazard to a patient who harbors one, even though he may for many years be unaware of its presence. In a review of the literature, two interesting cases of umbilical fistula due to Meckel's diverticulum were encountered. Neither of these, however, resembled the case we are reporting. In one of these cases, Ratnayeke reported the successful repair of a fecal fistula due to a patent vitelline duct in a six-week-old infant. In the other case<sup>3</sup> a draining umbilical sinus developed in a healthy twenty-year-old man. At the time of operation the sinus was found to communicate with a sac situated under the umbilicus. The sac proved to be a remnant of the distal end of the vitelline duct. There was no connection between the sinus and the ileum in this case.

#### SUMMARY

We have reported an unusual complication of a meckelian diverticulum. This was the occurrence, in a 75-year-old patient, of an external fecal fistula

which presented at the umbilicus and which communicated with the ileum through a persistent vitello-intestinal duct. The diverticulum had caused no symptoms prior to the patient's last illness. We were unable to find, in the literature, record of a previous similar complication in Meckel's diverticulum.

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# CHYLOUS MESENTERIC CYST\*

## Case Report

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WHEN CONSIDERING the differential diagnosis of an abdominal mass, it is customary to include a mesenteric tumor among the possibilities. A brief review of the literature will show that such tumors are among the rarest of abdominal neoplasms. Furthermore a chylous cyst is one of the rarest of mesenteric tumors. Some idea of its rarity may be obtained from the statistics assembled by Slocum<sup>7</sup> which show that only six cases were recorded at the Massachusetts General Hospital from 1900 to 1926; only one case was noted in over 93,000 admissions at the University of California Hospital and the Los Angeles General Hospital had only one case in over 188,000 admissions. While these figures are from reports of over ten years ago, the frequency of this condition has not increased. A recent case report by Beahrs and Judd<sup>1</sup> states that there have been seven cases at the Mayo Clinic in more than one million patients. The case which I am reporting is the first one recorded at the Jewish Hospital in over 160,000 admissions since our modern recording system was started 20 years ago.

It is important to specify what is meant by a chylous mesenteric cyst as much confusion exists in the literature. Various types of mesenteric cysts are described which need not be enumerated, but the chief confusion exists between a true chylangioma and an enterocystoma due to cystic dilatation of a congenital duplication of the bowel. This differentiation is most important according to Ladd and Gross<sup>5</sup> because they are pathologically different and require different forms of treatment. The duplication is a thickwalled structure which has all the intestinal layers in its wall. It usually lies immediately adjacent to the bowel between the folds of the mesentery and the musculature of the duplication is so intimately associated with that of the intestine that they cannot be separated without injury to the latter. The blood supply of the duplication is the same as that of the adjacent intestine so that the duplication cannot be removed without destroying the intestinal blood supply. The true mesenteric cyst on the other hand, is thin-walled and has no muscular coat or mucosal lining. While it may lie against the mesenteric surface of the intestine, there is a cleavage between the two so that it can usually be excised without injuring the bowel or its blood supply. These cysts could arise by obstruction of a lymphatic trunk, but the absence of demonstrable inflammation or other fibrosing lesion in the mesentery in such cases leads Ladd and Gross to doubt this theory. They believe that these cysts develop from misplaced bits of lymphatic tissue which proliferate and then accumulate fluid because they do not possess communications with the remainder of the lymphatic system. The source of the chylle in these cysts has not been definitely determined.

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Dowd<sup>2</sup> in a classic paper believed that it was an effusion into a preformed cyst because the rich anastomosis of peritoneal lymphatics seems to preclude cyst formation by obstruction to even many channels. On the other hand Ewing<sup>3</sup> is of the opinion that they are true chylangiomas due to congenital or acquired obstruction of lacteals.

Like many other types of cyst, these lesions seldom cause marked symptoms until complications develop. The most common complication is partial intestinal obstruction with its accompanying cramping pain. When this develops in the presence of a palpable mass, it is likely that a torsion of a tumor would be suggested, whereas, due to its location between the mesenteric leaves, these cysts rarely become twisted. In addition to intestinal obstruction which is common (30 to 50%) and torsion which is rare, Thompson and Chambers<sup>8</sup> state that other complications include peritonitis secondary to obstruction or rupture, hemorrhage into the cyst, rupture of the cyst either spontaneously or due to trauma, and incarceration of the cyst in the pelvis. In cases where complications have developed there is little time for delay so that an accurate diagnosis is seldom made before operation. However, when it is safe to take time to make leisurely studies Hinkel<sup>4</sup> believes that roentgenologic methods are of value. In three patients he was able to localize the lesion by studying its relations to the surrounding structures. This is done by giving a barium meal or enema followed by roentgenoscopic palpation of the lesion.

When confronted with one of these rare lesions the surgeon has a choice of several procedures. Most authors agree that the ideal solution is enucleation of the cyst from the mesentery if this can be done without interference with the blood supply to the bowel. According to Roller<sup>6</sup> the mortality of such treatment is 9 per cent whereas if it is necessary to add intestinal resection, the mortality is tripled. In some cases it may be inadvisable to attempt to remove the cyst either with or without intestinal resection and in these instances the sac may be marsupialized. The recovery rate after such operation is high but there may be a persistent sinus, although in several cases reported the sinus closed within a reasonable time.

#### REPORT OF CASE

A single girl, age 17, was admitted to the Jewish Hospital on the evening of October 29, 1947 complaining of abdominal pain. On the preceding day she had felt tired and slept poorly. She awoke with a pain around the umbilicus and ate little breakfast. The pain continued all day although her bowels moved and there was no nausea or vomiting. Her temperature and pulse were normal. Examination on admission revealed a mass in the mid lower abdomen which was not movable and was dull on percussion. No tenderness was present over the appendix but there was moderate tenderness over the mass. Bimanual examination by rectum, after catheterization of the bladder, revealed the uterus to be normal size and anterior and a mass about the size of a large orange was situated above the uterus. This was thought to be an ovarian cyst, probably dermoid and since there was abdominal pain, it was thought that partial torsion had occurred. Operation was advised.

*Operation.*—The abdomen was opened through a low right paramedian incision and a cystic mass was exposed at once. Examination of the pelvis showed normal pelvic

organs and the mass was not arising from the pelvis. Attempts to deliver the cyst from the wound were not successful until the wound was enlarged upward. After extending the incision, the mass was delivered along with several loops of lower jejunum. It was then determined that it was a cyst between the leaves of the mesentery with the small bowel stretched over the periphery. It was decided to attempt enucleation and an incision was made along the left leaf of the mesentery perpendicular to the bowel. The wall of the cyst was so thin that it was perforated and about a pint of milky fluid was expelled. The edges of the cyst were grasped with hemostats and the cyst wall was separated from the leaves of the mesentery. The cyst was unilocular and extended down to the mesenteric root. It was enucleated without interference with mesenteric vessels and the incision in the mesentery was closed with a continuous catgut suture. The abdomen was closed in layers without drainage. The convalescence was uneventful and she was discharged from the hospital on November 9, 1947.

**SUMMARY.**—Chylous cyst of the mesentery has an incidence of one case to 150,000 hospital admissions. It is seldom diagnosed before operation since it usually causes no symptoms until important complications arise. The true mesenteric cyst must be differentiated from the enterogenous cyst secondary to duplication of the bowel since the surgical problems involved are different. The manner in which the chyle enters the cyst is speculative. The ideal treatment is simple enucleation but intestinal resection may have to be done in addition. If the cyst wall cannot be removed with safety it may be marsupialized with reasonable hope of cure. A case is reported in which a simple enucleation was done with prompt recovery.

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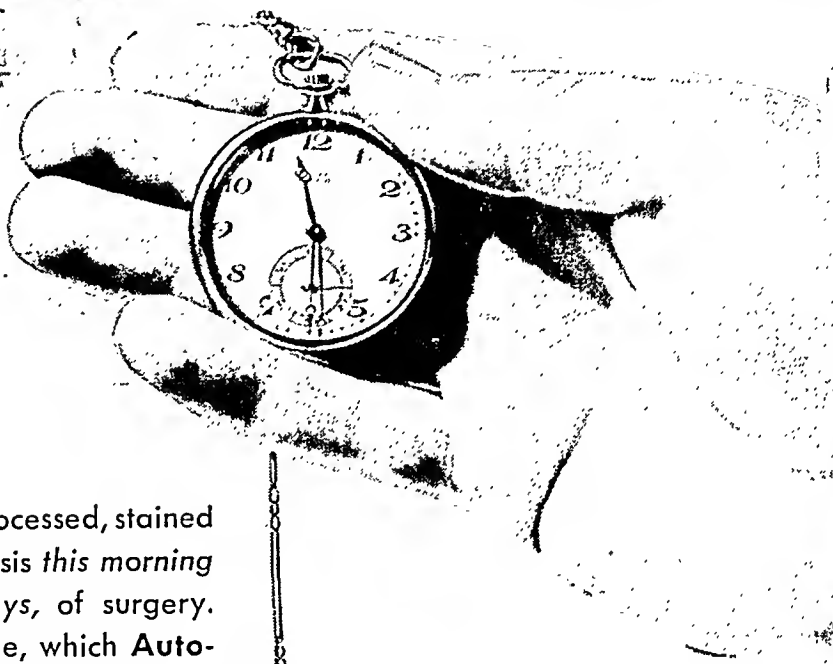
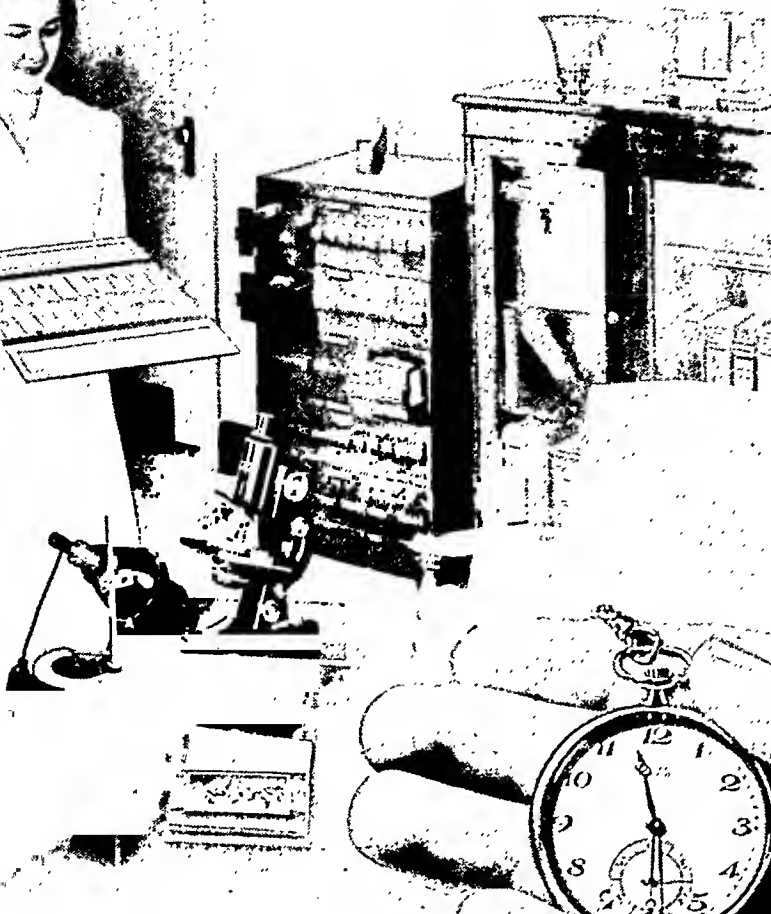
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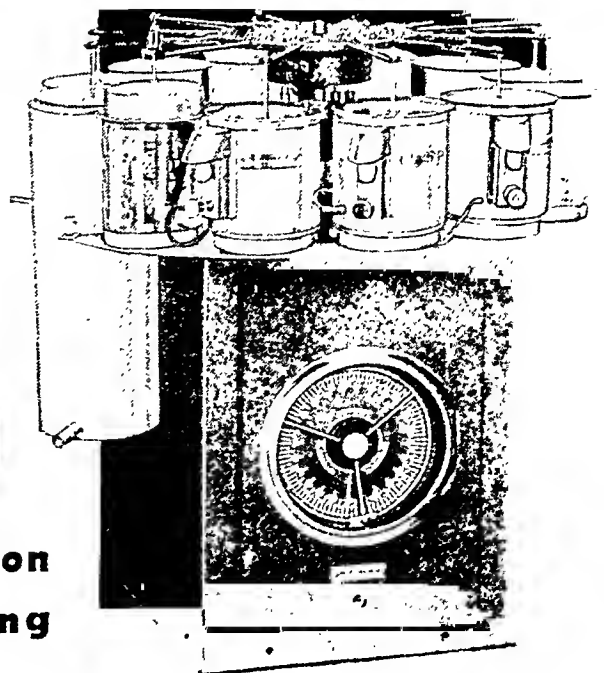
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## CAUSALGIA FOLLOWING GUNSHOT INJURIES OF NERVES\*† Role of Emotional Stimuli and Surgical Cure through Interruption of Diencephalic Efferent Discharge by Sympathectomy

JAMES C. WHITE, M.D., WILLIAM W. HEROY, M.D.,  
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"PERHAPS FEW PERSONS who are not physicians can realize the influence which long-continued and unendurable pain may have upon both body and mind. . . . Under such torments the temper changes, the most amiable grow irritable, the soldier becomes a coward, and the strongest man is scarcely less nervous than the most hysterical girl. . . . Nothing can better illustrate the extent to which these statements may be true than the cases of burning pain, or, as I prefer to term it, causalgia, the most terrible of all the tortures which a nerve wound may inflict." These comments were made by Weir Mitchell<sup>25</sup> in 1872, following an account originally written while he was seeing almost daily numbers of men suffering from gunshot wounds inflicted during the Civil War.

During the World War I not much progress was made in treating this condition, beyond the discovery that certain procedures were of little value. These included neurolysis, repeated resection of neuromata, proximal section of the affected nerve trunk or its chemical block, periarterial sympathectomy,\*\* and division of the posterior spinal roots. In the major causalgias,<sup>3</sup> excluding rare and almost exceptional instances, all failed to give the hoped-for-relief. To make matters worse, the burning pain often persisted for years, so that

\* This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

† Submitted for publication, September 1947.

\*\*In addition to the earlier European reports, which have been summarized by Leriche,<sup>38</sup> Homans<sup>14</sup> and Fontaine and Herrmann<sup>12</sup> in this country have recorded a few successful results from this operation in the atypical minor causalgias, Südeck's atrophy, etc. Leriche, although advocating periarterial sympathectomy as a preliminary procedure, admits a considerable number of failures (4 out of 10). In cases of severe diffuse post-traumatic neuralgia, he has concluded that this operation is generally ineffective. A similar conclusion has recently been expressed by Ulmer and Mayfield,<sup>39</sup> in whose hands this operation was ineffective.

TABLE I.—Summary of 13 Cases of Causalgia Treated by Preganglionic Sympathectomy.

Case	Wound	Paralysis	Distribution of Pain	Time of Onset After Wounding	Hyperpathia	Trophic Changes	Temperature of Extremity	Sweating	Relation to: Cold, Emotion	Neurosurgical Procedures in Addition to Sympathectomy	Result of Sympathectomy on Causalgic Pain
1. Chas. R. Pfc. USMC	Small shell fragments L. upper arm.	Median nerve (partial)	Entire hand.	Few hours.	+++	+++	Cool.	+++	+++	Early median neurectomy without improvement.	Complete relief, now plays strenuous games. Followed for 7 mos.
2. Chas. M. Pfc. USMC	Rifle bullet through arm above elbow. Artery injured.	Median and ulnar nerves, complete at first, later spontaneous recovery.	Entire hand.	After operation for aneurysm.	++	+	Cold.	++	++	Ligation of brachial artery 2 weeks after wounding.	Complete relief.* Followed 9 mos.
3. Norman C. Pfc. USMC	Machine gun bullet passed between bones of upper forearm.	Median and radial nerves (partial).	Entire hand.	Few hours.	++	+++	Cool.	++	++	Previous neurectomy and partial suture of median and radial nerves with partial relief.	Complete relief. Followed 3 mos.
4. Fred S. Pvt. USMC	Shell fragments upper arm and forearm.	Median nerve (partial), ulnar nerve (complete).	Entire hand.	5 hours.	+++	++	Cool.	+++	+++	Subsequent median neurectomy and ulnar nerve suture.	All hyperpathia cleared.* Followed 1 year.
5. John H. Maj. USMC	Upper humerus fractured by shell fragment. False aneurysm in axilla.	Median nerve (complete), ulnar nerve (partial).	Entire hand, but most marked in ulnar area.	Immediate.	++	+	Cold.	++	++	Ligation of axillary artery. Median nerve sutured later.	Complete relief. Followed 1 year.
6. Robt. B. Cpl. USMC	Bullet wound brachial plexus, fractured clavicle, severed subclavian artery.	Median (complete), ulnar nerve (partial), musculocutaneous and medial antebrachial cutaneous nerves (complete).	Entire hand, most severe in ulnar area.	1 week.	+++	++	Cool.	0	++	None.	Complete relief. Followed 8 mos.

\* See footnote on next page.

# CAUSALGIA FOLLOWING NERVE INJURIES

TABLE I (Continued)

Case	Wound	Paralysis	Distribution of Pain	Time of Onset After Wounding	Hyperpathia	Trophic Changes	Temperature of Extremity	Sweating	Relation to: Cold, Emotion	Neurosurgical Procedures in Addition to Sympathectomy	Result of Sympathectomy on Causalgic Pain
7. Nathan V. Pvt. USMC	Rifle bullet through upper forearm with fracture of ulna.	Median nerve (partial).	Median distribution.		++	+++ (median area).	Cold.	++	++	Neurolysis median nerve without relief.	Complete relief. Followed 5 mos.
8. Harold O'S. Pfc. USMC	Shell fragment wound of internal condyle of elbow.	Ulnar nerve (partial).	Ulnar area of hand.	Immediate.	++	+	Cold.	++	++	Previous ulnar neurolysis without benefit.	Complete relief. Followed 5 mos.
9. Howard W. Pfc. USMC	Bullet wound below elbow.	Median nerve (partial).	Median area of hand.	Immediate.	++	+	Cold.	++	++	Previous median neurolysis without improvement.	Complete relief. Followed 5 weeks.
10. Alfred D. Pfc. USMC	Mortar wound median side of shoulder, axilla to mid arm.	Median nerve (partial), musculocutaneous (complete).	Median area of hand.	Day after wound.	+++	+	Cool.	+	++	Block of brachial plexus without relief.	Complete relief. Followed 13 mos.
11. Wm. M. Cpl. USMC	Phosphorus grenade fragments in lower leg.	Posterior tibial and common peroneal (partial), tarsal nerve (complete).	Entire foot and toes.	Immediate.	+++	++	Cold.	++	++	None.	Incomplete sympathectomy failed to relieve pain in anterior third of foot. Satisfactory improvement following completion of sympathetic denervation and neurolysis. Follow-up period of 12 months.*
12. John B. GM 2/c	Razor slash across palm.	Median nerve paralysis at first complete, then partial recovery.	Median area.	6 months after wound with nerve recovery.	++	+	Cold.	++	++	Immediate median nerve suture.	Satisfactory relief.* Followed 3 mos.
13. John McC. Lt. (ig) USNR	Penetrating wound of lower thigh.	Posterior tibial (partial), and common peroneal nerves.	Sole of foot, especially on medial side.	Immediate.	+++	+	Cool.	+	++	None.	Complete relief. Followed 2 mos.

\* Residual paresthesia and hyperesthesia of a different type connected with recovery of the injured sensory axones (see discussion).

\*\* Patient 10 had such severe exacerbations of pain in his hand on swallowing anything cold that he was only able to sip warm liquids. This most unusual complaint was relieved immediately following procaine block and disappeared permanently after preganglionic sympathectomy.

... Patient 11 complained of increase in his pain on urination and defecation, a feature which has previously been commented upon. This complication has been relieved by sympathectomy.

when John Mitchell reviewed the subsequent history of some of his father's cases in 1895 he found a considerable number who had continued to suffer permanently. Leriche<sup>18</sup> also has recorded a case of 17 years' duration. In a few cases the burning pain undoubtedly subsides with time and spontaneous or surgical repair of the injured nerve, but the interval is often so long that irreparable changes have taken place in the skin, muscles, bones, and, most serious of all, in the individual's psychic constitution. As a result drug addiction, deterioration of the personality, and ultimate suicide have been frequent terminal results.

In the 1920's progress in therapy began with the discovery of effective methods of sympathetic denervation of the limbs. The work of Leriche in Strasbourg, which is best summarized in his book on "The Surgery of Pain,"<sup>18</sup> was a great stimulus, and it is to him, more than to any other, that credit is due for pointing out the role of the sympathetic nervous system in the causalgic syndrome. Sporadic favourable results of surgical interventions on the sympathetic ganglia were also published by Spurling,<sup>35</sup> Ross,<sup>32</sup> Kwan,<sup>17</sup> Livingston,<sup>20</sup> and others. During World War II rapid strides were made, especially by British and American surgeons. It has now become apparent that the classical syndrome of major causalgia, with related emotional and autonomic manifestations, can be treated by early sympathetic denervation of the arm or leg with consistent success. Case reports to back up this statement have been published by Doupe, Cullen, and Chance,<sup>9</sup> Mayfield and Devine,<sup>22</sup> Spiegel and Milowsky,<sup>34</sup> Rasmussen and Freedman,<sup>28</sup> Tyson and Gaynor,<sup>38</sup> Albritten and Maltby,<sup>2</sup> and Ulmer and Mayfield.<sup>39</sup> The following series of 13 cases gives added confirmation and emphasizes the role played by the sympathetic nervous system.

#### CLINICAL PICTURE OF CAUSALGIA

The clinical picture of major causalgia with burning pain in the hand or foot, trophic changes in the skin, subcutaneous and bony structures, and autonomic stigmata of excessive vasomotor and sudomotor activity is so well known (Leriche,<sup>18</sup> Livingston,<sup>20</sup> de Takáts<sup>36</sup>) that it will not be discussed here. As Livingston has pointed out, it is unfortunate that so many observers, including Mitchell himself, have included so many conditions with burning pain as the only point in common under the diagnosis of causalgia. Other conditions causing persistent pain and hyperesthesia after nerve wounds have recently been discussed by White;<sup>41</sup> Südeck's atrophy, so-called reflex dystrophy, post-traumatic arthritis, and neuralgia in amputation stumps should be definitely excluded from this classification. In our opinion the term causalgia should be limited to include only the sequelae to penetrating wounds of the extremities, which cause injury to the nerve trunks and the triad of burning pain, trophic changes, and autonomic phenomena. This is such a distinct clinical entity that there should be no difficulty with its differential diagnosis.

As regards the vasomotor changes, some observers, notably Mitchell<sup>25</sup> and de Takáts,<sup>36</sup> have been struck by the tendency to local warmth and

vasodilatation,\* but this phenomena is certainly not a constant one. Livingston<sup>20</sup> has taken exception to this view, as he found relatively few instances where a local rise in temperature was a persistent feature. More often, when it does occur, it is transient and is followed by a fall in temperature so that the involved part becomes colder than normal. In Ulmer and Mayfield's<sup>39</sup> series they found 35 patients with cold and 40 with hot extremities, whereas in our group all 13 patients had cold and moist extremities (see Table I). Perhaps the difference may arise in the date at which these individuals are first examined. Mitchell must have seen his Civil War wounded and de Takáts his civilian patients at an early date, whereas our sailors and marines evacuated from distant outposts in the Pacific required longer time to reach the hospital than the European wounded treated by Mayfield and his associates. While de Takáts<sup>36</sup> has shown by oscillometric tracings that the vasodilator response is unilateral, the vasoconstriction and abnormal sweating which we have observed usually involve the other extremities as well, although often to a lesser degree. It is quite possible that cutaneous vasodilatation is the characteristic condition in the early phase of causalgia, but after a time at least the opposite is most frequently the case. Everyone who has studied the condition in the recent war wounded has been impressed by the profuse sweating of the involved hand or foot, but nervous sweating of the palms and soles is a common phenomenon in wounded men, especially when pain or worry are prominent features.

The principal purpose of this paper is to emphasize the importance of thermal and emotional factors on aggravation of pain, and the effectiveness of sympathectomy in its relief. In order to bring out the salient factors on which the etiology of the condition depends and the rationale of eliminating the efferent sympathetic discharge to the painful limb, we plan to present our clinical data first and to discuss their implications afterwards. For convenience, the most important features of each case are summarized in Table I and further details are given in the brief case histories of each of the 13 patients which follow.

#### CASE HISTORIES

**Case 1.**—Charles R., 21 years, Pfc., U.S.M.C.: On Okinawa on 5/1/45 this private received multiple wounds from a "booby trap" in the head, right thigh, and left upper arm. Within a few hours he noticed the onset of burning pain in the left hand, together with a sense of partial numbness in the second and third fingers. All his wounds healed uneventfully. On 6/18/45 at another hospital the median nerve was explored and minor adhesions freed, without the least benefit. On admission to the U. S. Naval Hospital at St. Albans on 7/16/45 he complained of constant diffuse burning pain in the entire hand and lower forearm, which was increased by cold, sudden noises, and any form of apprehension. He could not tolerate the minor disturbances on the open ward, and he kept his hand constantly moist with a wet towel or by immersion in a basin of lukewarm water (Fig. 1A.)

---

\* In a previous article one of us<sup>41</sup> attempted to explain pain during states of vasodilatation, as well as during constriction, to the overactivity of sympathetic vasodilator fibers. Such fibers have been postulated on the basis of observations made by Lewis and Pickering,<sup>19</sup> but the recent work of Sarnoff and Arrowood<sup>33</sup> has made this hypothesis untenable.



FIG 1A—Case 1. Preoperative photograph of patient guarding painful left hand and soaking it in lukewarm water.



FIG 1B—Postoperative photograph showing free use of formerly sensitive hand.

He was suffering so much that he begged for early relief. Accordingly diagnostic paravertebral procaine block was performed on the day after his admission. The nervous apprehension caused by this procedure resulted in such severe throbbing pain that it was necessary for a hospital corpsman to drip lukewarm water over the lower arm and hand while the needles were being inserted in his back. However, within a minute of the time the infiltration of procaine began the discomfort disappeared, and a few minutes later the cold extremity became warm and dry. That evening he went to the movies for the first time, but noticed some recurrence of his pain. Left thoracic preganglionic sympathectomy was performed two days later, followed by complete relief. He got up on the first postoperative day and was able to move out on the open ward and use his hand without discomfort (Fig. 13.) Shortly thereafter he began to play volley ball and other strenuous games, and was then discharged from the Marine Corps to enter civilian work.

Case 2.—Charles M., 19 years, Pfc., U.S.M.C. On 2/28/45 at Iwo Jima this marine was struck by a bullet in the right upper arm and flank. The bullet, which traversed the lower third of his arm, caused a partial injury of the median and ulnar nerves, nicking

the brachial artery as well. Eleven days later the resulting aneurysm was operated upon at Pearl Harbor. Immediately afterward he began to complain of burning pain deep in the hand, made worse by cold, touching the extremity, or by excitement such as that caused by watching a baseball game or by a close call in an automobile. On arrival at St. Albans he had a cold hand without any radial pulse, the characteristic signs of median and ulnar paralysis, and severe ischemic fibrosis of the flexor muscles in his forearm. On 8/21/45, a week after his admission, following temporary relief obtained by paravertebral procaine block, his moderately severe causalgia was relieved by preganglionic sympathectomy. Although the relief of his burning pain and hyperesthesia was complete and the hand became totally dry, there was little increase in temperature in the anesthetic median and ulnar areas (see below under discussion). Since this operation he has been hospitalized for a period of six months for plastic procedure to release scar tissue contractures in his forearm and elbow. No operation on the injured nerves has been necessary because of their spontaneous regeneration. We have been interested to observe that with early return of sensation he has developed the usual mild cutaneous hyperesthesia that accompanies nerve regeneration, but without any trace of his previous burning pain. This has been a common finding in other cases.

Case 3.—Norman C., 23 years, Pfc., U.S.M.C.: A machine-gun bullet passed through the left forearm on 1/5/45, causing partial paralysis of the median and radial nerves. Five hours later, on recovering from anesthesia for débridement of the wound, he began to suffer from causalgic pain through his hand. Neurolysis and partial suture of both partially paralyzed nerves had been performed four months prior to his admission to St. Albans, and this had resulted in some improvement in his burning pain, but he still complained of severe stabbing, shooting pain in his wrist and hand. This was made definitely worse by cold weather but was not related to emotion. We regarded this as a somewhat atypical case of causalgia, but we obtained satisfactory relief by diagnostic procaine block. Preganglionic sympathectomy, performed on 9/5/45, has been followed by a complete remission of all his complaints. During the three months that have elapsed since operation there has been only partial vasodilation in the residual hypesthetic territory of the median nerve (see below under discussion).

Case 4.—Frederick S., 19 years, Pfc., U.S.M.C.: Multiple wounds in the right upper and lower arm were received at Okinawa on 5/10/45 (Fig. 2) with partial median and complete ulnar paralysis. His burning pain began five hours after he was wounded. Next to Case 1, this patient had the most severe causalgia of the entire series. When he was admitted to St. Albans in July the burning pain involved his entire hand. This became much worse in the cold and quite unbearable on any psychic disturbance, so that he lay in a quiet, darkened room with his arm immobile on the bed (Fig. 2A) and usually protected by moist towels. He complained particularly of the aggravating effect of loud noises, jarring of the bed, exciting movies or any other psychic stimuli, of cold draughts of air over his hand or cold, rainy weather. The patient stated that each night when he got quieted down and relaxed his pain largely disappeared and he was able to sleep well, but it would appear again soon after he awakened. At the time of his admission he unfortunately had a complicating infectious hepatitis, so that we did not dare submit him to general anesthesia and operation until his jaundice cleared. During this period of waiting his causalgia was relieved three times by paravertebral procaine infiltration of the upper thoracic ganglia, only to recur within a few hours on each occasion. Finally sympathectomy was performed on 9/19/45 and his causalgia disappeared from this date.

A week later the nerves in his arm were widely exposed and a long gap in the ulnar repaired by transplantation and suture. Figure 2B shows the complete injury to the ulnar nerve and the surrounding adhesions of the median, which undoubtedly gave rise to the causalgic syndrome. In the forearm there were only fine adhesions to each trunk. Following suture the patient made excellent progress in nerve regeneration at the rate of



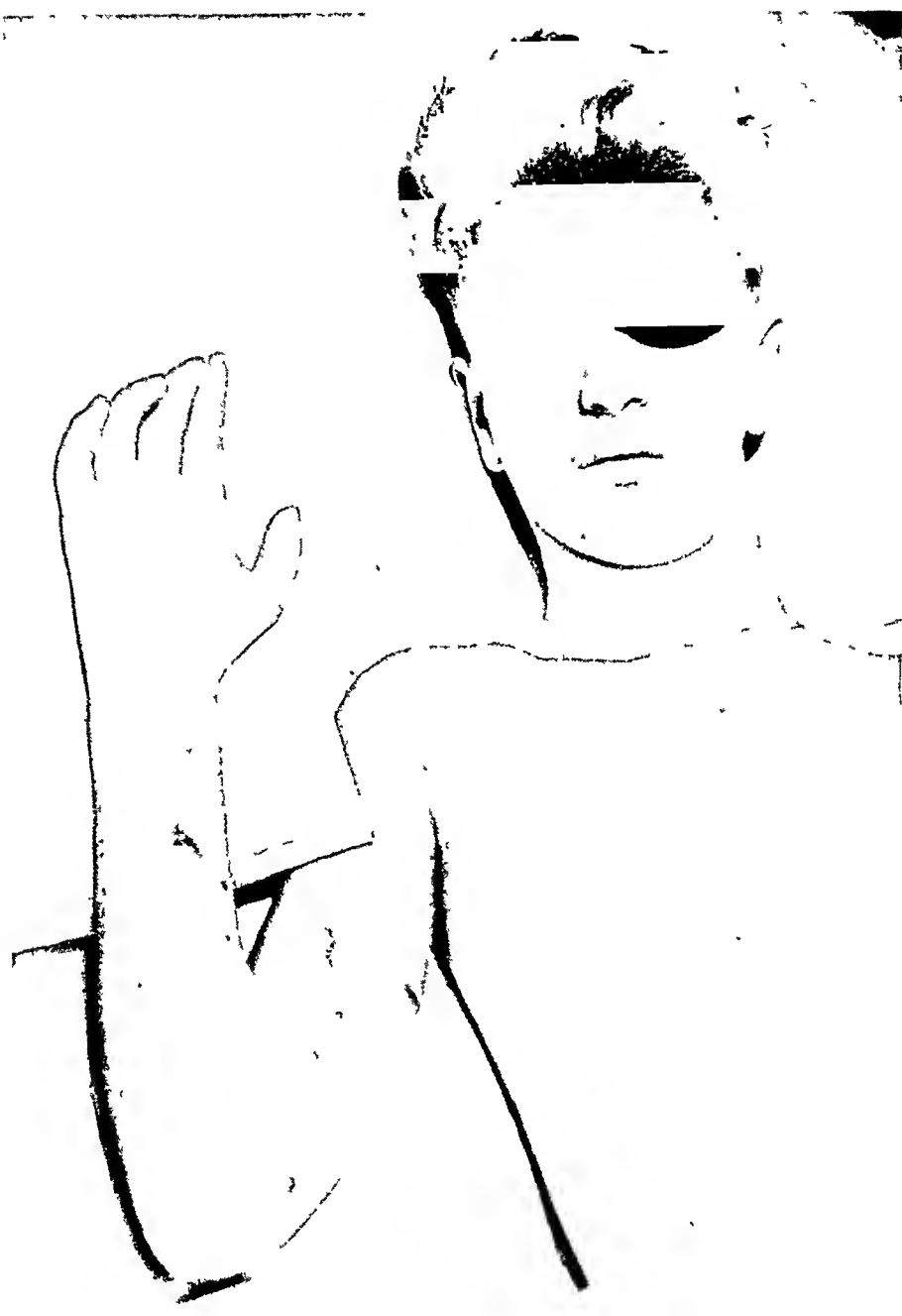


FIG. 2A.—*Case 4.* Preoperative photograph of patient to illustrate wounds in arm and characteristic position in which patient kept it immobilized. Hand was usually protected by moist towel. Note moisture of palm and trophic changes.

3.5 mm per day. It is again of interest to note that, whereas vasodilation of the median area was complete following preganglionic sympathectomy (skin temperature of the first three fingers in a room at 67° being between 86.5° and 90°), the temperature in the hemianesthetic ring finger measured 90° on the median and 86° on the ulnar side, and in the completely denervated little finger, where there was complete degeneration of the post-

ganglionic sympathetic fibers, was reduced to 74°. (See discussion below. He has been under observation for one year and remains free of his former burning pain.

**Case 5.**—John H., 25 years, Maj., U.S.M.C.: This officer was struck by shell fragments at Okinawa at 5/4/45, from which he sustained a compound fracture of the surgical neck of the left humerus and other injuries of lesser importance. The missile, which entered his axilla, partially divided the axillary artery and ulnar nerve, and severed the median. Severe causalgic pain developed immediately throughout his entire hand. On admission to St. Albans he was in poor general condition and still had an unhealed wound in his left axilla. This soon began to extrude clots of blood so that it was necessary to ligate the axillary artery on 9/15/45 to prevent serious hemorrhage. This operation permitted evaluation of the nerve injury, but median suture in the presence of sepsis was out of the question. It was of interest that this patient, in addition to noticing an increase

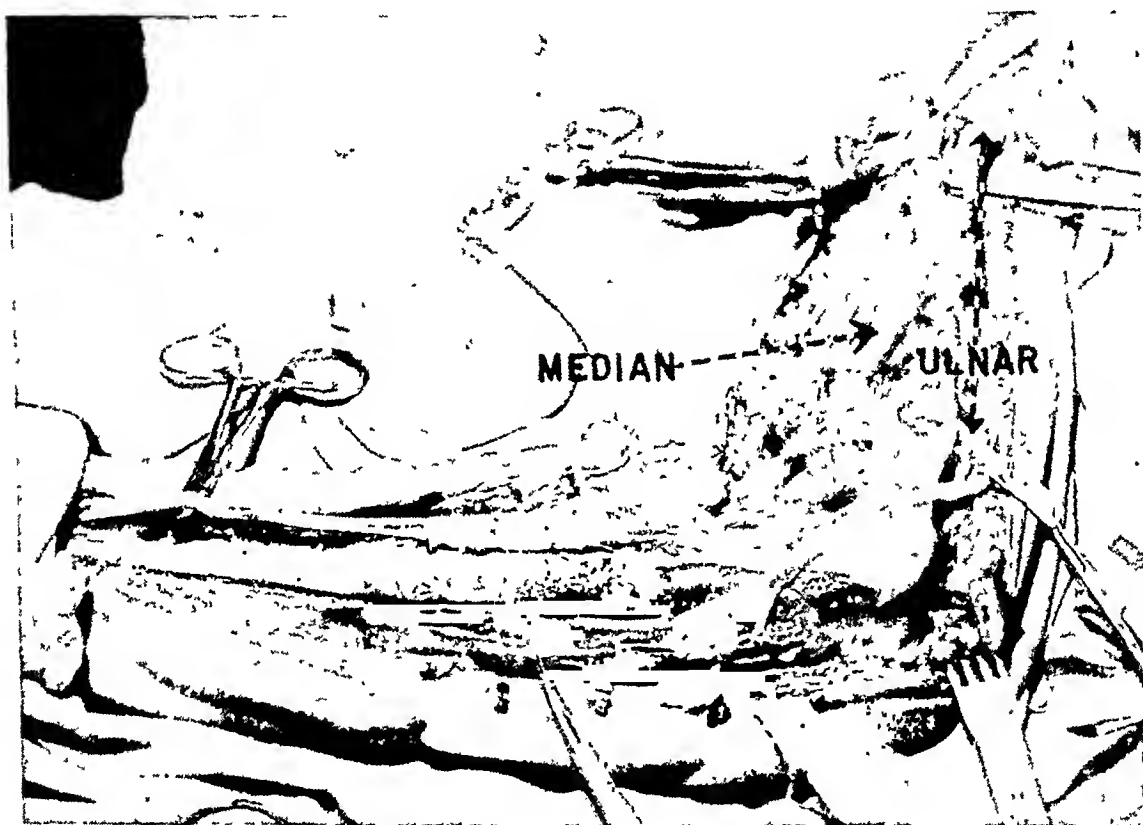


FIG. 2B.—Photograph taken at secondary exploration preliminary to suture of severed ulnar nerve. Note wide gap in ulnar and lateral neuroma of median nerve. In lower forearm neither median nor ulnar nerves were injured. The median is shown elevated by the hemostat.

in his burning pain on cold and psychic stimuli, complained bitterly of the throbbing pain in his hand during any slight argument or whenever his children cried. Following diagnostic block, thoracic sympathectomy was performed on 9/27/45 and has produced an excellent result to date (12 months). His median nerve was sutured on 3/6/46, a month after final healing of his wound. In this patient, as in Cases 2, 3, and 4, there was no vasodilatation in the cutaneous area of the median nerve, where the postganglionic sympathetic fibers had degenerated from the injury to the nerve trunk (skin temperature of first three fingers averaging 72°, but 90° in fifth finger). The physiologic reasons for this phenomenon are given below (see discussion). He remains free of pain at the end of a year.

**Case 6.**—Robert B., 23 years, Cpl., U.S.M.C.: On 6/19/45 this patient had received gunshot wounds resulting in compound fractures of the left clavicle and right femur.

There was an accompanying partial paralysis of the brachial plexus and injury to the subclavian artery. Emergency treatment consisted of débridement without direct exposure of the nerves. His causalgic pain developed a week after his injury. On admission to St Albans he complained of constant hyperpathia with intense throbbing on exposure

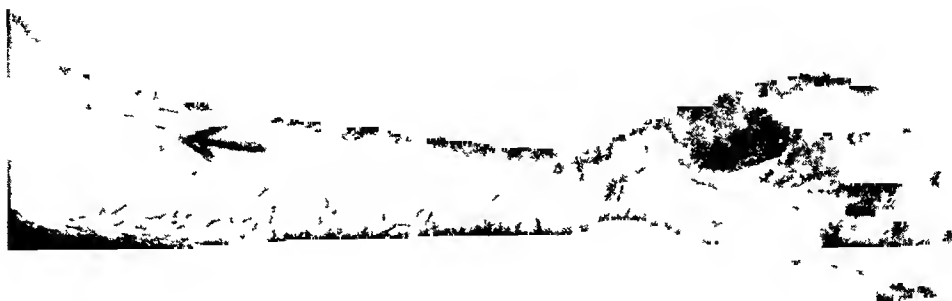


FIG 3A.—Case 7. Photograph showing trophic changes in skin and tapering of fingers in area innervated by median nerve. The arrow points to bullet wound.



FIG 3B.—Appearance of median nerve at preliminary exploration. Note filmy cicatricial adhesions.

(This figure is reproduced with the permission of the *American Journal of Surgery*, where it was first published by White<sup>1</sup>.)

to cold and psychic stimuli (loud noises, vibrations, annoyance, or excitement). There was paralysis of the musculocutaneous and median nerves, the ulnar being less extensively involved. The causalgic pain, as is so commonly the case, was in the area of the incompletely paralyzed ulnar nerve. After successful procaine block, an upper thoracic preganglionic sympathectomy was performed on 9/27/45, which has resulted in com-

plete relief of his causalgic pain. At the end of eight months there has been good spontaneous recovery of both nerves, with fair return of function in the proximal group of muscles controlled by the median.

Case 7.—Nathan V., 28 years, Pfc., U.S.M.C.: A rifle bullet through the left elbow at Iwo Jima on 3/4/45 caused a slight injury of the median nerve. In this patient the area of burning pain, cutaneous trophic changes, and tapering fingers were limited to the territory of the injured nerve (Fig. 3A). For this reason a neurolysis of this nerve was performed first (Fig. 3B), but without any relief. Diagnostic procaine block and subsequent thoracic sympathectomy gave most satisfactory results.

Case 8.—Harold O'S., 22 years, Pfc., U.S.M.C.: On 3/11/45 a shell fragment caused a partial injury of the right ulnar nerve at the internal condyle. The patient began to notice causalgic pain as soon as he recovered from an accompanying cerebral concussion. When he was admitted to St. Albans he suffered from moderately severe burning pain and hyperesthesia in the ulnar area of his hand, aggravated by cold and the usual psychic factors. The first attempt to block his upper thoracic sympathetic ganglia resulted in vasodilatation, but failed to produce satisfactory drying of the skin or any Horner's sign; furthermore, his pain was not relieved. Following a second, effective diagnostic block and throughout the five months he was under observation following surgical preganglionic denervation he remained free of pain.

Case 9.—Howard W., 30 years, Pfc., U.S.M.C.: This patient received a through-and-through bullet wound between the two bones of the right upper forearm on 9/21/44 at Peleliu. With the partial injury of his median nerve he noticed immediate onset of causalgia limited to the area supplied by this nerve. On 3/26/45 the nerve was explored and freed of adhesions, but without significant effect on his pain, which remained fairly troublesome eleven months after the receipt of his wound. Following a diagnostic chemical block, a preganglionic sympathectomy was carried out on 19/29/45. This has produced very successful warming of his cold hand and effective relief of his pain.

Case 10.—Alfred D., 22 years, Pvt., U.S.M.C.: This man was injured by fragments of mortar shell explosion in the upper arm on 9/16/44 at Peleliu. There was complete paralysis of the musculocutaneous and partial of the median nerve. Severe causalgic pain appeared in the area of its palmar distribution the day after he was wounded. He described this pain as intense burning and throbbing in the thenar side of his hand, which was increased by any light touch or rub, or by any sudden noise, mental upset, fright, anger, or excitement. Instead of being aggravated by cold, this patient complained particularly of hot weather, when he had to protect his hand by ice or cold, wet packs. The most striking feature of all was the relation of his pain to any attempt to swallow cold liquids. This began a month after his wounding and forced him to limit his fluid intake to sips of warm milk. Brachial plexus block with procaine at another hospital had failed to relieve his pain, but the result from paravertebral infiltration of the sympathetic ganglia in our hands was excellent. For the first time he was able to drink a tumbler of cold water. Preganglionic thoracic sympathectomy, performed on 11/14/45, gave a most satisfactory result. At the end of thirteen months he has no further complaints and is very happy to be able to drink cold liquids, especially beer. In spite of residual biceps paralysis, he has good use of his arm, which has now recovered normal sensation in the hand and a fair degree of elbow flexion through compensatory ("trick") movement by the brachioradialis muscle.

Case 11.—William M., 20 years, Cpl., U.S.M.C.: This Marine Corps corporal was struck on 5/5/45 by a phosphorus grenade, which resulted in multiple wounds of the knee and lower leg with complete paralysis of his sural and a partial injury of his right peroneal and posterior tibial nerves. Immediately afterwards he noticed extremely disagreeable burning pain throughout his foot, except in the anesthetic area on its lateral aspect. At the time of his admission the burning pain and hyperesthesia were intense and were greatly augmented by cold or psychic factors. In addition, his knee

was ankylosed in extension and his foot contracted in a severe equinus position. The sole of his foot and toes were deeply incrustated in brownish desquamating skin, which could not be washed off on account of the pain. His pain was also increased during urination and defecation. The patient was unable to walk or to think of anything beyond his painful condition. We felt so certain that sympathectomy would bring about adequate relief that the operation was done on 11/26/45 without preliminary injection of procaine. In this operation through the retroperitoneal approach two well defined ganglia and 2.5 cm. of the lumbar chain were removed below the crus of the diaphragm.

Although the immediate result was encouraging, the patient began to complain of recurrent burning pain and hyperesthesia in his toes and the ball of his foot on the third day. The result in the posterior two-thirds of his foot remained satisfactory, but the anterior third soon became as painful as ever. On careful inspection, however, it



FIG. 4.—Case 11, after preliminary incomplete sympathectomy. Areas of residual sweating demonstrated by Victor Minor's starch-iodine test and outlined by dotted lines. The dark area in the toes and anterior foot corresponded exactly with the patient's residual hyperpathia.

was evident that there were tiny drops of sweat on the toes. Residual sudomotor activity was confirmed by Victor Minor's starch-iodine test<sup>23</sup> (Fig. 4) and by the low cutaneous resistance to a galvanic current demonstrated by Richter's Dermometer.<sup>31</sup> On examination of the postoperative lumbar roentgenogram it was found that the lowest metallic marker clip was at the level of the upper portion of the third lumbar vertebra. It therefore seemed probable that the cause for the residual pain in the distal portion of this patient's foot was due to the presence of an undivided white ramus communicans connecting the spinal cord with the paravertebral sympathetic chain at an abnormally low level. This possibility was put to the test by paravertebral injection of procaine against the side of the fourth lumbar vertebra on two occasions, with complete disappearance of the persistent hyperpathia in the toes. On 1/4/46 the anterolateral surface of the third and fourth lumbar vertebrae was widely exposed through a midline abdominal incision with separation of the posterior peritoneum to the right of the vena cava and common iliac vessels. Another 3 cm. of sympathetic trunk was removed, including a large ganglion situated a centimeter above the point where the trunk disappeared beneath the iliac vessels. Two months after this added resection of the lower lumbar chain the patient was distinctly improved. It was then possible to manipulate all his toes, which were formerly too sensitive to permit washing the skin or cutting the nails. Trophic changes in the skin cleared. The burning pain on cold and psychic stimulation also disappeared. At 12 months, after added neurolysis of the injured nerves, he is free of pain and receiving orthopedic rehabilitation for his stiff knee and the contraction deformity in his foot.

**Case 12.**—John B., 19 years, GM 2/c, USN: An injury of the median nerve in the palm of his right hand was caused by a razor slash received on 6/2/45. Suture of the severed median nerve at the base of the palm was performed an hour later and the incision healed well. During the period of complete paralysis the patient experienced no pain. At the end of six months, however, with partial reinnervation of the palmar and digital median branches, severe burning and hyperesthesia developed in this portion of the hand. These sensations became much worse on exposure to cold or emotional

excitement, and he noticed them particularly when he went to exciting movies or to a shooting gallery. At these times sweating was also greatly increased in the ulnar area of his right hand, and in the left also, though to a lesser extent. Following thoracic preganglionic sympathectomy on 2/6/46 all the intense burning pain has disappeared. Cold and excitement no longer induce disagreeable throbbing and burning. With partial sensory recovery to the base of the first three and a half fingers the sense of paresthesia and less intense hyperesthesia, which characteristically accompany nerve recovery, are still a source of mild complaint. These residual sensations, however, in no way resemble his former incapacitating causalgic pain. Two weeks after his sympathectomy the median nerve was re-explored and freed of scar tissue. With its gradual regeneration and the redistribution of myelin around the sensory axones the quality of sensation should return to normal.

Case 13.—John McC., 28 years, Lt. (j.g.) U.S.N.R.: On 3/27/45, while flying over Iwo Jima, this pilot was struck by a fragment of flak which passed transversely through the posterior portion of his left thigh at the level of the hamstring tendons. There followed immediate foot drop and aching, burning pain in the sole of his left foot. This became difficult to bear before he was able to land his plane. There was no injury to the popliteal artery and his wound healed without infection. During the next 12 months, prior to his admission on the neurologic service, his causalgia was a constant source of severe pain and total incapacity. It was made much worse by all the usual cold and psychic stimuli, and also whenever he laughed. He found that he was more comfortable when he wore a thick wet sock or one impregnated with vaseline. At times, when the pain became particularly severe, he would immerse his foot in a bucket of cool water. When put in a room next to the galley, the noises were so troublesome that he had to be moved. He obtained more relief from a stiff drink of whiskey than from an injection of morphine.

On examination a year after his injury it was found that there was considerable spontaneous recovery of the peroneal and a residual partial damage to the posterior tibial nerve. The burning hyperesthesia involved the sole of his foot, especially in the area of the medial plantar nerve.

Paravertebral lumbar procaine block was followed by complete temporary relief and a restoration of normal sensation. Following lumbar sympathetic ganglionectomy on 3/22/46, he was up on the fourth day and has been fully relieved of his pain (2 months observation).

#### DISCUSSION

In giving our clinical data first we have purposely not adhered to the usual order of a medical paper, because the findings recorded in Table I and the individual case histories have so much bearing on the etiology of causalgia and its surgical treatment, which we intend to discuss in the light of the clinical observations presented above.

#### INCIDENCE

No statistics are available as to the rate of incidence of causalgia in previous wars, but in the present conflict Ulmer and Mayfield<sup>39</sup> have reported 75 cases amongst 1477 peripheral nerve injuries at the Percy Jones General Hospital; Spiegel and Milowsky<sup>34</sup>, seven cases in 275 soldiers at another U. S. Army Hospital; and we have seen this complication 13 times in some 400 sailors and marines with wounds of the peripheral nerves at the U. S. Naval Hospital in St. Albans. This represents a rate of incidence after penetrating wounds of nerves in the range of 2.0 to 5 per cent.

## ETIOLOGY

Many aspects of the causalgic syndrome suggest that it is a form of psychoneurosis, and this diagnosis has often and most unfairly been applied to these victims. The fact that the whole pseudo-neurotic picture so often clears immediately following suitable surgical intervention, when the sufferer has lost his dread of pain, no longer requires sedatives, and can resume a normal life, indicates that the personality disturbance is a result rather than the cause of an unendurable condition. This is well illustrated by our first patient. Prior to his sympathectomy he had become a neurotic recluse and remained almost motionless in a quiet room with his arm protected by a moist towel. He was so preoccupied with his painful hand that he was able to think of nothing else. Immediately after operation, however, he joined the other men on the open ward, became carefree and gay, and was soon able to take part in strenuous games. In the past, when no successful treatment was known, causalgia was a frequent cause of drug addiction and often led either to deterioration into hopeless invalidism or to self destruction. Psychologic studies made on service personnel after successful treatment in the recent war (Mayfield and Devine;<sup>22</sup> Spiegel and Milowsky<sup>34</sup>) and in civilians (de Takáts<sup>36</sup>) have not brought to light any predisposing psychogenic factors.

In reading through Mitchell's fascinating monograph on "Injuries of Nerves" and also the earlier account of Mitchell, Morehouse and Keen<sup>26</sup> one gains the impression that causalgia was much more common in the War between the States than in either the first or second World Wars. On first thought it would seem likely that this is due to the decreasing rate of wound sepsis. Mitchell pointed out that "every possible precaution should be taken to lessen the chance of deep inflammation and the secretion of pus." Certainly there has been a far lower incidence of sepsis in the gunshot wounds of the recent war, but nevertheless we have seen severe causalgia in several patients where the wound healed per primam. Furthermore, the usual early onset of causalgic pain is strong evidence against the etiologic importance of sepsis. One of the most impressive features about our cases was the rapidity with which burning pain developed after the wound. In all but two of the 13 patients in whom the exact time of onset is recorded it began during the first day, and most of the men noticed it either at once or within the first few hours. Leriche<sup>18</sup> and Ulmer and Mayfield<sup>39</sup> have also noticed the frequent, almost immediate onset of causalgia. This eliminates not only sepsis but also ascending neuritis (so frequently mentioned in older accounts), anoxia due to fibrosis, and compression of the nerve by scar tissue or neuroma formation. There have been occasional reports indicating that at times the pain may be caused by the proximity of a foreign body, but we have recently removed a considerable part of the movement of a wrist-watch from a Marine Corps officer's median nerve where there was no history of pain at any time. Livingston,<sup>21</sup> however, has described the relief of median nerve causalgia in a Marine private wounded at Guadalcanal following the removal

of a shell fragment from the upper arm. In this case movement of the metallic fragment produced shocks along the course of the nerve. Under such circumstances it is logical to remove the foreign body, but neurolysis with freeing of adhesions and transplantation of the nerve into a healthier tissue bed has rarely influenced the pain (see Cases 1, 3, 7, 8, 9 and Fig. 3B).

In addition to the factors listed above, injury to a major blood vessel has been cited as a possible cause of burning pain. Leriche<sup>18</sup> reports relief of pain following excision of the traumatized sections of arterial trunks, but in our cases only three out of 13 patients had coexistent arterial injuries. None of Ulmer and Mayfield's<sup>39</sup> large series are reported as having associated wounds of major arteries.

Our cases summarized in Table I and the recent reports of other neurosurgeons in the American and British Armies<sup>2, 10, 22, 28, 34, 38</sup> have shown the effectiveness of sympathectomy in the relief of causalgic pain. Case 11, in whom the first incomplete lumbar sympathetic ganglionectomy gave only partial relief, lost the burning hyperpathia in his toes after remaining lower sympathetic connections were interrupted. The effectiveness of sympathectomy casts an interesting light on the etiology of causalgia. In spite of the belief held by some writers, notably Kuntz and Saccomanno,<sup>14</sup> that sensory fibers reach the spinal cord along the sympathetic nerves, the great majority of the anatomic, physiologic, and clinical evidence is against this.\* Kuntz's experiments were performed on cats and it is not certain that section of the spinal cord between the second and third lumbar spinal segments would eliminate all somatic efferent connections from the lower extremity, especially on stimulation of the femoral nerve or application of a tourniquet above the knee. Furthermore, why should reduction of the stream of efferent sympathetic motor impulses which occurs in a quiet environment, after the ingestion of alcohol, in sleep, and during bouts of fever reduce causalgic pain? These individuals soon learn that they are most comfortable in a warm, quiet room and must avoid psychic stimulation of any sort. We were at first much surprised by the increased comfort of our patients during the quiet hours of the night, when sleep greatly reduces the activity of the sympathetic centers in the hypothalamus. Mitchell commented on this also, stating that "it is quite rare for a patient to arouse from sleep with pain, and I have heard men remark that it took some time to get awake to the pain." Patient 13 of our series stated that a moderate amount of alcohol gave him more comfort than an injection of morphine. Fever induced by intravenous foreign protein and by general heating of the body also reduces efferent vasoconstrictor tone. Mayfield and Devine<sup>22</sup> have observed several striking remissions of causalgic pain after periods of malarial chill, which should have no effect on pain

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\* Since this manuscript was submitted, one of us (J.C.W.) has stimulated the second and third lumbar ganglia in the course of resection of the sympathetic chain under local anesthesia. The patient, an intelligent observer suffering from pain in a thigh amputation stump, reported ipsilateral low abdominal and pelvic pain, but no reference whatsoever to his leg.



transmission but would result in reduction of vasoconstrictor discharges from the hypothalamus. This is also true of the new drug tetraethylammonium bromide, the pharmacologic action of which has recently been investigated by Acheson and Moe.<sup>1</sup> From a recent clinical study by Berry, Campbell, Lyons, Moe, and Sutler<sup>5</sup> and in further unpublished reports by Campbell,<sup>8</sup> it is clear that this compound, which blocks the synapse between the sympathetic pre- and post-ganglionic neurones, but has no effect on sensory fibers, will effectively stop the burning pain of typical causalgia following nerve injury. On the other hand, causalgic pain is aggravated by any increase in these tonic impulses, such as occurs in cold, damp, or very hot weather, or during psychic irritation. Quoting again from Mitchell's account: "The constitutional condition, reacting on the wounded limb, exasperates the hyperesthetic state, so that the rattling of a newspaper, a breath of air, the step of another across the ward, the vibrations caused by a military band, or the shock of feet in walking, gives rise to increase of pain."

It is our contention that the "hyperesthetic state" is both caused and aggravated by autonomic impulses, released at the hypothalamic level in response to thermal and psychic stimuli, and distributed over efferent sympathetic neurones.

We have recently requested our patients to write down the irritative environmental factors which convert the ever-present sensation of burning pain and hyperesthesia into a state of throbbing torture. The list includes the following interesting statements:

Cold, damp or very hot weather.

Cold air on the hand.

Loud or unexpected noises, annoying radio programs.

Jarring of the bed.

Anything exciting such as a narrow escape, a harrowing movie, stirring music, etc.

Children crying.

Hypodermic injections into any part of the body.

Arguments with other patients.

Physical exertion.

Defecation and urination (Case 11 only).

Drinking anything cold (Case 8 only).

Laughing (Case 13 only).

All of these different factors were known to Mitchell, except the stimulus of cold liquids, which was so striking in Case 8, laughing, and the irritating effects of the radio and cinema. Although Mitchell did not connect these facts, it is now obvious that the single common denominator which underlies all these diverse irritants is the burst of sympathetic impulses which are emitted under such circumstances from the hypothalamus and cause vaso-motor, pilomotor, and sudomotor responses in the extremities, particularly in the areas of the hand and fingers, and in the toes and soles of the feet. These

are the areas where autonomic activity, which produces nervous sweating and vasoconstriction, is most in evidence; furthermore, these identical stimuli would produce alterations in digital blood flow, if measured by the plethysmograph.

Doupe, Cullen, and Chance<sup>10</sup> have gone so far as to ascribe the peculiar qualities of causalgic pain to direct cross stimulation of sensory fibers by efferent sympathetic impulses at the point where the nerve trunk is injured, rather than to the indirect action of the vasoconstrictor response which they also produce. They have cited most convincing evidence for this activation of sensory fibers by sympathetic impulses. Their theory furnishes an explanation not only for the increase in pain which so characteristically takes place in a cold environment, but also for that occurring during any form of emotional excitement, cutaneous stimulation, and, in some extreme instances, during everyday visual and auditory stimuli. Burning pain in causalgia and in certain other conditions occurs in direct relationship to the tonic vasomotor, sudomotor, and pilomotor discharge over the sympathetic efferent pathways. It is reduced in a quiet, stable environment and during sleep, when the tonic hypothalamic discharge is greatly diminished, and can be interrupted completely by tetraethylammonium bromide for as long a period as the ganglionic synapses are blocked by the drug. There is no valid evidence that the sympathetic system plays any direct role in the central conduction of the painful stimuli.

As further corroboration of this theory of sympathetic activation of sensory fibers, it has been shown by Katz and Schmitt<sup>15</sup> that under certain circumstances efferent nerve impulses can alter the excitability of adjacent sensory axones. Recently Granit, Leksell, and Skoglund<sup>13</sup> have given direct experimental proof of such cross-stimulation between motor and sensory fibers at a point of nerve injury by recording with the cathode ray oscillograph an afferent discharge from the sensory root which takes place when the motor root is stimulated. They conclude that the small, poorly myelinated pain axones of the C-group should be especially susceptible to "fiber interaction," and that this is a simple explanation for some of the symptoms of causalgia. The theory of Doupe and his co-workers assumes that the activating impulses come from the sympathetic vasomotor, pilomotor, and sudomotor discharge, which is always increased by cold or emotional excitement. A serious objection to this theory has been brought forward by Richards,<sup>30</sup> who points out that proximal division of the nerve has failed to relieve causalgia, although it must necessarily eliminate both the efferent and afferent arcs of the "short-circuited" area at the level of nerve injury. Possible flaws in this pertinent objection are that (1) neurectomy, which was often attempted unsuccessfully in the past, was performed at too late a date, after the painful pattern had become established in the sensory cortex (as is now known to occur after long-standing pain from a phantom limb); and (2) when a nerve trunk is involved in the causalgic state its sensory fibers may become so irritable

that a similar "short-circuiting" mechanism will be set up in the proximal neuroma after neurectomy at a higher level. Ulmer and Mayfield<sup>39</sup> have recently reported successful results from excision of the injured segment of nerve with immediate suture.

#### TREATMENT

Our experience, as well as that of other writers previously mentioned, has shown that total sympathetic denervation of a limb is an effective method for the relief of true causalgia. A single partial failure in Case 11 turned out to be due in large part to an incomplete operation. Here a limited sympathectomy of the type recommended by Atlas,<sup>4</sup> with removal of two ganglia at the side of the second lumbar vertebra, failed to eliminate the burning pain in the toes and anterior third of the foot, although the hyperesthesia of the proximal two-thirds was relieved. When the sympathetic denervation was completed by removing an abnormally-placed ganglion below, the residual pain in the anterior portion of the foot gradually disappeared. In another instance of slightly atypical causalgia in the hand, which we had the opportunity to observe, but which is not included in this series, there was also an early recurrence of pain after sympathectomy. In this case postoperative roentgen rays revealed that the surgeon had mistaken the fourth for the third rib and, by making his approach at such a low level, had failed to interrupt the important sympathetic efferent fibers which leave the thoracic cord in its second anterior root. It is therefore obvious that, as in every other condition which can be influenced by sympathectomy, the surgical denervation of the area concerned must be complete if it is to be effective.<sup>43</sup> In view of these findings we have come to believe that, in the early typical case of major causalgia which exhibits the classical triad of symptoms described above and in which there has been temporary relief of pain following diagnostic procaine block, failure is due to incomplete sympathetic denervation. Under such circumstances residual vasomotor and sudomotor activity should be sought, not by the cruder methods of recording environmental alterations in skin temperature and gross sweating, but by the digital plethymograph<sup>7</sup> and changes in cutaneous resistance to galvanic current.<sup>31</sup>

The technical steps necessary to obtain a complete sympathetic denervation of the upper or lower extremity are described in White and Smithwick's monograph on *The Automatic Nervous System*<sup>43</sup> and, with more recent modifications, in White's chapter on the surgical technic of sympathectomy in Bancroft and Pilcher's *Surgical Treatment of the Nervous System*.<sup>40</sup> For the relief of burning pain in the hand the preganglionic operation is best. On theoretical grounds we would have supposed that resection of the inferior cervical and upper two thoracic ganglia would have given equally effective results as far as relief of pain is concerned, but this has not been the experience of Rasmussen and Freedman.<sup>28</sup> In addition, the latter procedure, by causing degeneration of the postganglionic neurones, does not produce as effective vasodilatation of the hand<sup>42</sup> and also leaves the patient

with a disfiguring unilateral Horner's syndrome. After wounds in the lower leg removal of the second and third lumbar ganglia should ordinarily suffice, but it is best to remove a good five centimeters of the chain and carry the resection down to the lower border of the third lumbar vertebrae.\* Excision of too short a length of trunk may be followed by regeneration, and our unfortunate experience in Case 11 shows that at times white rami communicantes may reach the ganglionated chain below the second lumbar vertebra.

The area of sympathetic denervation must also reach well above the level of nerve injury. Whereas the standard upper thoracic sympathectomy interrupts sympathetic impulses to the entire arm and shoulder, it must be borne in mind that after resection of the second and third lumbar ganglia the effect is limited to the foot. When the pain arises from a wound at the knee it is advisable to remove the first lumbar ganglion as well, and in cases of nerve injury in the upper thigh it may be necessary to extend the sympathectomy upwards through the diaphragm to include the lowest thoracic ganglia as well.\*\*

In general it is wise to test the effectiveness of sympathectomy by preoperative paravertebral injection of the regional sympathetic fibers. This should stop the sense of burning and hyperpathia for a period of several hours. While procaine injection alone may occasionally produce long-standing relief in some of the minor causalgias, in painful post-traumatic arthritis and Südeck's atrophy, there are only a few cases on record<sup>28</sup> where it has stopped major causalgia for more than a few hours. It does, however, assure the surgeon of the successful outcome of the proposed sympathectomy and is, therefore, of particular value in cases that are in any way atypical. Possibly the recent demonstration of Rasmussen and Farr<sup>27</sup> that prolonged duration of chemical block can be obtained by the injection of 5 per cent benzyl alcohol propylaminobenzoate with procaine (Rectocain) may permit effective therapy by paravertebral injection alone.

The operation for causalgia in both the upper and lower extremities is simple and safe in the hands of a surgeon who is experienced in the technic of sympathetic neurosurgery. Furthermore, the postoperative period of disability is short and the patient need only spend a few days in bed. There have been no significant complications in any of these patients. There is therefore every reason to operate at an early date before the patient has become dependent on narcotics, and particularly before he has developed neurotic tendencies or irreversible atrophic changes in his bones and soft

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\* In performing these operations it has always been our practice to apply a dural clip to the proximal and distal stumps of the resected portion of the sympathetic trunk and to each large ramus cut. The position of these metallic markers compared with the bony landmarks in postoperative roentgenograms gives an accurate picture of the anatomic extent of the sympathetic denervation.

\*\* While this point is not yet fully established, recent observations of Ulmer and Mayfield<sup>39</sup> render it highly probable.

tissues (see protocol of Case 11 above). Once the causalgic syndrome has developed with full intensity there is little, if any, hope of spontaneous remission. It has been our experience that preliminary neurolysis is totally ineffective for relief of severe causalgia, and that this procedure, if indicated, should be undertaken after the burning pain has been relieved by sympathectomy. In five of our patients (Nos. 1, 3, 7, 8, and 9) neurolysis of the injured nerve had been performed as the primary procedure (Fig. 3B), but without any influence on the causalgia. We therefore recommend primary local surgery only if there is a foreign body in contact with the nerve, a septic focus, or when the pain is so mild that the patient can bear it without too great difficulty over the long period required for complete reneurotization of the injured nerve. Ulmer and Mayfield<sup>39</sup> have reported that complete resection of the area of injured nerve followed by suture may be expected to abolish the pain, but as the injured nerve which produces the causalgic syndrome is rarely seriously damaged and, given time, will recover spontaneously, this radical procedure will rarely be justified.

Two final points connected with these operations are of considerable theoretical interest. These are related to the physiologic changes that follow injuries to the sympathetic and sensory fibers in the peripheral nerves:

(1) A number of our patients (Nos. 2, 3, 4 and 5) had, in addition to a partial injury of the median or ulnar nerve, complete paralysis of the other trunk. After sympathectomy under these circumstances there was complete vasodilatation only in the area of intact peripheral nerve supply, the paralyzed median or ulnar area remaining equally dry but distinctly cooler and somewhat cyanotic. The explanation for this lies, in large part at least, in the sensitization phenomenon, whereby denervated smooth muscle becomes hypersensitive to circulating adrenaline and sympathin. This, as shown by White, Okelberry, and Whitelaw<sup>42</sup> and by Ascroft,<sup>3</sup> is far more noticeable in areas where the postganglionic sympathetic neurones have degenerated. As these lie within the peripheral nerves, added interruption of the preganglionic connections by a paravertebral sympathectomy cannot result in a complete release of vasospasm. This phenomenon, which is of considerable academic interest, has been thoroughly investigated by Doupe<sup>9</sup> and Richards.<sup>29</sup> The chemical sensitivity of denervated smooth muscle to circulating sympathomimetic hormones may greatly reduce the value of sympathectomy in restoring a satisfactory circulation in Raynaud's disease, but fortunately does not vitiate its beneficial effects on pain. Here all that is necessary is the complete interruption of the efferent sympathetic discharge which arises in the hypothalamus in response to psychic and environmental factors.

(2) Although we have found that the intense burning hyperpathia of causalgia, which is increased by thermal and emotional disturbances, is effectively relieved by sympathectomy, the paresthesia and milder hyperesthesia which accompany sensory regeneration are not necessarily relieved by this operation. These abnormalities in the quality of returning sensation are of common occurrence after peripheral nerve injury; they are not gen-

erally severe, and they disappear with more complete recovery. They do not appear to be influenced in any way by hypothalamic stimulation and increase of the sympathetic discharge. The disagreeable quality of sensation during the early phase of nerve recovery has been ascribed by Trotter<sup>37</sup> and more recently by Bigelow et al<sup>6</sup> to the lack of insulating myelin sheaths around the regenerating sensory fibers, so that these naked axones function as pain fibers and react to any stimulus in an explosive fashion. Foerster,<sup>11</sup> on the other hand, has explained the hyperesthesia as due to a lack of sensory inhibition which maybe a normal function of the larger myelinated fibers in the posterior roots. In either case, the mild tingling and disagreeable sensations found in an area with early sensory recovery tend to disappear as the regenerating sensory fibers mature and reacquire their myelin sheaths. On careful testing and questioning of these patients we have discovered some degree of residual hyperesthesia in the areas of sensory recovery in Cases 2, 4, 6, 11, and 12. It was described as only a mild residual discomfort by four of these patients, but in Case 11 was severe enough to retard his rehabilitation.

#### SUMMARY AND CONCLUSIONS

1. Major causalgia, as first described by Mitchell, Morehouse and Keen,<sup>26</sup> follows partial injury of the mixed peripheral nerve trunks incurred in penetrating wounds with a rate of incidence somewhat under 5 per cent. The typical triad of symptoms consists of hyperpathia (a disagreeable burning pain with intense hyperesthesia in the hand or foot), trophic changes, and autonomic stigmata of excessive vasomotor and sudomotor activity.

2. The pain is aggravated to an unbearable degree by factors which increase the sympathetic discharge from the hypothalamic centers—thermal and psychic stimuli. While it may disappear with complete regeneration of the injured nerve, this process is at best so slow that the patient is liable to become addicted to morphine, suffer serious personality changes, and develop irreparable trophic disturbances in his bones, joints and soft tissues.

3. Interruption of the sympathetic outflow, preferably by preganglionic sympathectomy, is an effective method of treatment and should be performed at an early date. Preliminary chemical blocking of the sympathetic rami and ganglia by injection of procaine is a valuable diagnostic test, particularly in atypical cases. Repeated paravertebral injections have been reported to give lasting relief in some cases, but they have not been effective in our patients.

4. Sympathectomy in our hands has resulted in consistent relief of the burning causalgic pain. After operation eight patients had no further complaints of any sort. On careful cross-questioning, five had some residual paresthesia and hyperesthesia in the area of recovering cutaneous innervation. This in no way resembled the former causalgic syndrome and was identical with the usual subjective sensations that accompany nerve regeneration. It was severe enough to retard rehabilitation in only a single patient.

5. It is our opinion that relief of burning pain following sympathetic denervation is due to elimination of the efferent sympathetic discharge from

the hypothalamic centers rather than to any interruption of pain fibers. There is no good evidence for the existence of centrally conducting sympathetic axones in the peripheral nerves. Furthermore, the suffering of causalgia is relieved under circumstances in which sympathetic tone is reduced—viz., a quiet, warm environment, ingestion of alcohol, sleep, and febrile states. Recently reported work on experimental animals suggests that there may be a short-circuiting effect in the area of the injured peripheral nerve which permits direct irritation of sensory afferent fibers by efferent sympathetic impulses.

6. Thirteen cases are described which have been treated at a Naval Hospital. All were relieved of their unbearable pain and the resultant effect on their psychological status and resistance to rehabilitation was dramatic. While the period of follow-up has been usually less than a year, there is no reason to suppose that recurrent complications will occur.

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## EFFECT OF VAGOTOMY AND OF DRUGS ON GASTRIC MOTILITY\*†

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RENEWED INTEREST IN VAGOTOMY for the treatment of peptic ulcer dates back to the report of Dragstedt and his co-workers<sup>1</sup> in 1943. Since that time preliminary reports of clinical use of this procedure have been made by Grimson,<sup>2</sup> Moore,<sup>3</sup> and Walters,<sup>4</sup> with their associates. Each observer early noted complications following vagotomy, particularly delayed emptying of the stomach. That gastric retention occurred after vagotomy in patients has long been known. As early as 1911, Exner<sup>5</sup> reported secondary gastroenterostomy after vagotomy in two patients because of "ill effects of paralysis of the stomach." It is now generally accepted that varying degrees of retention develop in most patients treated by vagotomy unless a gastroenterostomy is performed. Gastric retention has led to varying frequency of secondary operations.

Dragstedt and Schafer<sup>6</sup> reported gastrojejunostomy necessary in three of the first 15 patients. In their first communication, Grimson et al<sup>2</sup> reported secondary gastroenterostomy in three of 25 patients and in a recent report,<sup>7</sup> in six of 56 patients. Moore and associates<sup>3</sup> had only one patient in 33 who had secondary gastroenterostomy. Walters and his group<sup>4</sup> recently presented a series of 56 using various technics and frequently draining the stomach. One patient who had vagotomy and gastroenterostomy subsequently required jejunojejunostomy for retention. Harkins and Hooker<sup>8</sup> had one patient out of 26 who required secondary gastroenterostomy, and Sanders<sup>9</sup> had one in 50. Since many of the above patients had pre-existing gastroenterostomy stomas or drainage of the stomach at the time of vagotomy, it is evident that retention requiring secondary gastroenterostomy is not an infrequent complication. Retention not requiring surgical relief may produce symptoms. Dragstedt<sup>6</sup> stated that although symptoms of retention do occur they are insignificant whereas Grimson<sup>7</sup> described persistent serious symptoms of retention in 15 of 56 patients.

Most authors have attributed this retention to changes of gastric motility. In kymographic studies after vagotomy, Thornton, Storer, and Dragstedt<sup>10</sup> found decreased motility and concluded that gastric hypermotility and hyper-tonicity of ulcer patients returned toward a normal state after bilateral vagotomy. They believed that retention is caused by decreased tone and

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emphasized suction and residual aspiration as preventive measures. Grimson et al<sup>7</sup> performed kymographic studies of intragastric pressures in most patients before vagotomy and in 42 patients immediately afterward. Recordings were also obtained in 34 patients between three months and one year, and in 11 between one and two and a half years. They determined that the average resting intragastric pressure of patients who had vagotomy alone for duodenal ulcer was somewhat increased after vagotomy, whereas amplitude of gastric contraction waves decreased. These changes persisted in nine patients followed more than one year. They believe that retention is caused by a disturbance of the emptying cycle of the pylorus or an achalasia-like obstruction and not by lack of resting intragastric tone. Moore, Chapman, Schulz, and Jones,<sup>3</sup> however, concluded that gastric motility usually decreases after vagotomy but may return to normal or nearly normal levels at the end of one year. It is evident, therefore, that there is no agreement upon the explanation of the retention phenomena.

It is not possible in this report to review completely the extensive literature, experimental or clinical, on gastric motility and the effects of vagus nerve section. Excellent summaries are provided in the papers by Ferguson<sup>11</sup> and by McSwiney.<sup>12</sup>

Since retention with delayed gastric emptying occurs frequently after vagotomy and occasionally causes serious complications, studies were started nearly two years ago in animals and in patients to find, if possible, a non-operative means of treatment. Gastrometric methods were used for all observations.

#### METHOD

In rabbits, a thin rubber balloon was attached over the end of a small rubber catheter and passed into the fasting stomach. The tube was attached to a water manometer recording fluctuations of intragastric pressure on a kymograph and the balloon was inflated with an average of 25 cc. of air.

In dogs, a bromoform manometer was usually employed, the balloon being inflated with 200 cc. of air.

A similar method of recording was used in patients using a larger balloon over the end of a Levine tube connected to a bromoform manometer. Three hundred cc. of air were introduced into the balloon in increments of 50 cc. at about one minute intervals.

#### CHRONIC EXPERIMENTS ON VAGOTIMIZED ANIMALS

Fifty rabbits were subjected to vagotomy through a left thoracotomy incision using positive pressure ether anesthesia. The esophagus and vagus nerves were freed, a 2 cm. section of each nerve was removed, and smaller fibers if found were excised. Satisfactory postoperative recordings of gastric motility were obtained from eight hours to one year after operation in 26 rabbits.

Results of these studies are shown in Table I. It was hoped that vagotomy would produce a hypomotile stomach comparable to that seen in patients after vagotomy, in order that action of drugs which might restore contractions

could be studied. However, hypermotility usually developed and animals could not be used for this purpose. The arithmetic mean of the height of contractions preoperatively was 3.48 cm. of water, and postoperatively 4.8 cm. The arithmetic mean of the frequency of contractions preoperatively was 11.6 contractions per ten minute intervals and post-operatively was 19.9. A typical contrast between effect of vagotomy in patients and in rabbits is illustrated in Figure 1. Several observations in these animals, however, appear worth recording.

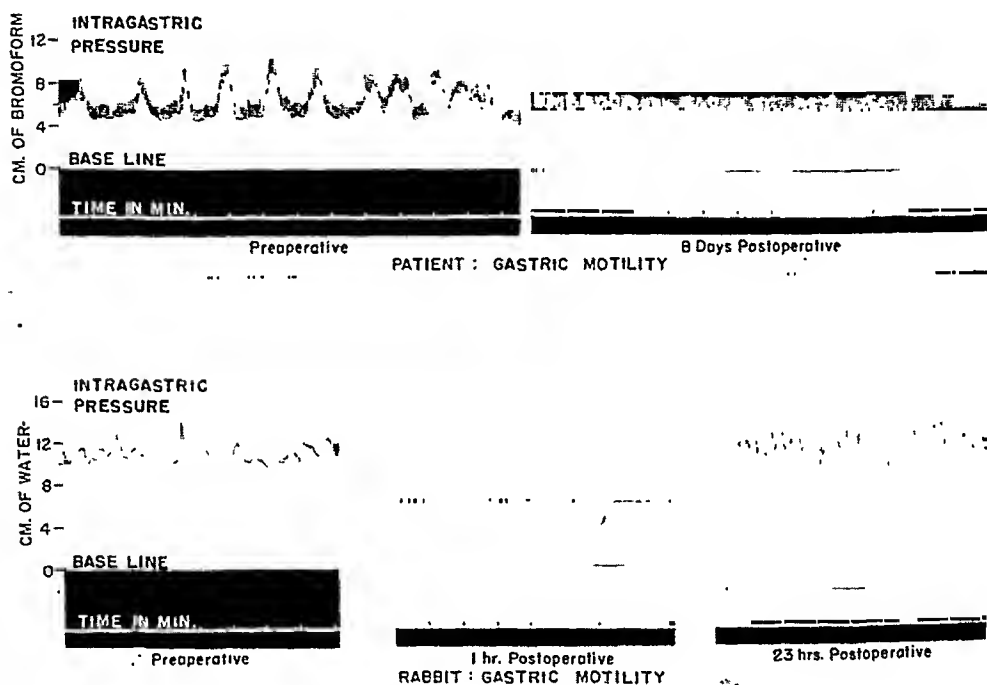


FIG. 1.—Tracings of fluctuations of intragastric pressure of a patient and of a rabbit are contrasted. Marked fluctuations occurred in the patient before vagotomy (upper left) and ceased afterward (upper right). Fluctuations of the rabbit (lower left) ceased during the first few hours after vagotomy (center) but by 23 hours (lower right) spontaneously became frequent and exaggerated.

Completeness of transthoracic vagotomy was tested two weeks or more after operation by acute experiments in 6 rabbits. Balloon study showed typical high rapid hypermotile waves at the start of each acute experiment. The vagus nerves were then again sectioned, this time in the neck, using local anesthesia. Hypermotility was not altered. Also, electrical stimulation of distal ends of the divided vagi produced no change. Atropine, 0.1 to 0.3 mg., given subcutaneously during recording of hypermotility in three other animals effected cessation of hypermotility. In one after 20 minutes and in another after 30 minutes motility ceased. In the third there was a marked decrease

TABLE I.—*Gastric Motility in 26 Rabbits After Transthoracic Vagotomy*

	Time After Operation			
	0 - 48 Hours	2 - 7 Days	8 - 30 Days	1 - 12 Months
No. Tests . . . . .	9	19	21	15
Absent Motility . . . . .	4	3	1	1
Normal Motility . . . . .	4	12	2	5
Hypermotility . . . . .	1	4	18	9

of contractions in 30 minutes. Two units of pituitrin were given intravenously to three other rabbits with hypermotility. This caused immediate loss of resting tone and cessation of contractions lasting six to ten minutes.

Three to ten units of insulin were given intravenously during recording of hypermotility in four additional rabbits surviving transthoracic vagotomy. Motility promptly stopped in each. Hypermotility returned after about 25 minutes and during the period of hypoglycemia. In one of these animals hypermotility developing after 25 minutes was slightly greater than that present before injection of insulin. Intravenous administration of 50% glucose in water a half hour or more after insulin and during the period of hypoglycemia stopped all motility. Control animals with intact vagi showed similar reactions to insulin hypoglycemia except that normal motility present before insulin increased during the period of hypoglycemia.

Autopsies were performed on most of the rabbits surviving transthoracic vagotomy. Grossly there was no evidence of overlooked nerves. Stomachs were uniformly markedly enlarged and contained huge quantities of sour greenish semi-solid residue. Gastric ulcers were present in one-fifth of the animals.

Transthoracic vagotomy was also performed on two dogs and their gastric motility was observed for two months. Complete emptying time of the stomachs was decreased, as judged by passage of barium seen fluoroscopically. Kymographic studies, which had revealed resting intragastric pressures of 38 to 40 mm. of bromoform and moderately irregular contraction patterns with rate varying from one to four per minute and excursions varying from 8 to 44 mm. of bromoform during three tests on each dog before vagotomy were definitely altered afterward. Average resting intragastric pressures after vagotomy were 57 and 69 mm. of bromoform. With two exceptions the pattern was markedly irregular. Frequency varied from one to six per minute and excursions ranged from 4 to 100 mm. of bromoform during 13 one- to two-hour balloon studies run at intervals of several days to two months. The two exceptions occurred at 16 and 39 days and differed in that contractions were regular, excursions varying from 2 to 4 mm. of bromoform and frequency varying from three to four per minute. At autopsy these two dogs weighing 10 and 12 kg. respectively had stomachs markedly distended, filling nearly half the abdomen. The volume of one stomach was 550 cc. and of the other 700 cc. Ulcer was not found in either.

Since these attempts to produce satisfactory chronic preparations with hypomotile stomachs failed in both rabbits and dogs, observations were carried

out to study gastric motility during the first 12 hours after cervical vagotomy and to determine effects of drugs during this period.

#### ACUTE EXPERIMENTS ON VAGOTOMIZED RABBITS

Observations were made in 48 rabbits before and during the first 12 to 48 hours after cervical vagotomy. Cessation of gastric contractions always occurred. Animals seldom survived more than 48 hours, usually dying with respiratory infections. Each of six that survived developed hypermotility

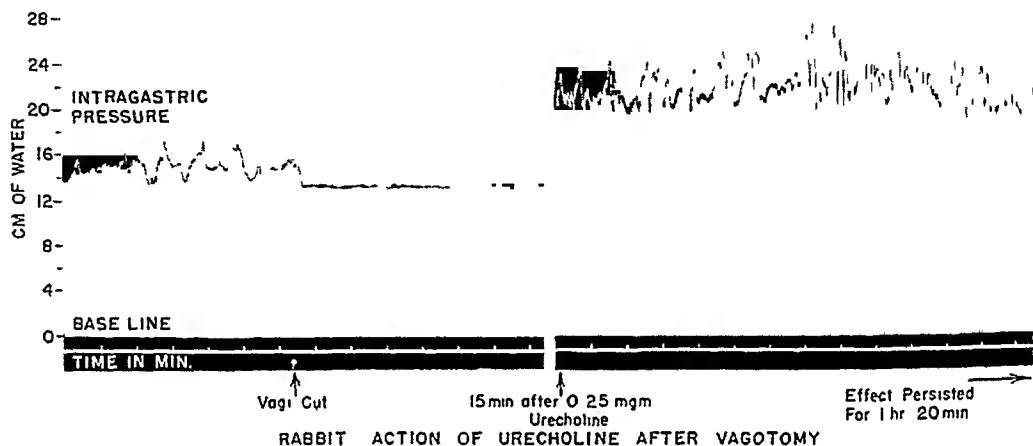


FIG 2.—Gastrometric tracings illustrating immediate effect of vagotomy (left) and increase of tone with restoration of forceful contractions (right) 15 minutes after intramuscular injection of urecholine.

like that described above under chronic experiments on vagotomized animals.

During the 12 to 48-hour period of absent motility after cervical vagotomy, insulin hypoglycemia in seven animals did not restore motility during two to nine hour periods of continuous observation. Also, gastric hypermotility produced by insulin hypoglycemia in four normal animals was immediately and completely abolished by cervical vagotomy performed one half to one hour after injection of insulin.

Drugs other than insulin were also given during the 12-to-48 hour period of absent motility. These drugs and their effects are summarized in Table II. Of the drugs used, pilocarpine, Doryl and Urecholine produced most effective restoration of contractions. A typical effect of Urecholine is illustrated in Figure 2.

#### STUDIES ON PATIENTS BEFORE AND AFTER VAGOTOMY

Before vagotomy four drugs were given during gastrometric study periods in 19 patients. Each patient had a peptic ulcer to be treated by vagotomy. Eight tests with Prostigmine (0.5 to 1.5 mg. subcutaneously), four with Mecholyl (0.2 Gm. orally), and four with Doryl (0.15 to 0.25 mg. subcutaneously or 2.0 mg. under the tongue) failed to alter frequency, or pattern of contractions. Urecholine (10 mg under the tongue) had no effect in two

TABLE 2.—*Effect of Drugs on Gastric Motility in Rabbits After Cervical Vagotomy*

Drug	No. of Animals	No. of Tests	Effective Dose	Increase of Tone	Restoration of Contractions
Pilocarpine .....	4	4	3.0 mg.	2 - 4 cm.*	4 - 6 cm.
Histamine .....	4	6	0.5 mg.	0 - 2 cm.	0 - 2 cm.
Prostigmine .....	5	6	0.2 mg.	0 - 2 cm.	2 - 4 cm.
Mecholyl .....	9	18	2.0 mg.	0 - 2 cm.	2 - 4 cm.
Doryl .....	9	17	0.02 mg.	2 - 4 cm.	4 - 6 cm.
Urecholine .....	7	12	0.25 mg.	0 - 2 cm.	4 - 6 cm.

\* cm. of water.

patients and was followed by slight increase of contractions in one. A similar slight increase was produced in another by 2.5 mg. subcutaneously.

Experimental observations of the effect of drugs were obtained in 91 instances, using patients at intervals of seven days to two and a half years after transthoracic vagotomy. During 15- to 60-minute periods of observation before administration of drugs, motility was absent in most patients and abnormally low in all. The postoperative tracing in the upper half of Figure 1 is typical. Drugs to be tested were then administered and observation recorded for several hours. Subcutaneous injection of 0.5 to 2.0 mg. of Prostigmine was employed in 21 tests on 16 patients. It was without demonstrable effect on gastric motility. Other drugs produced varying effects abstracted in Table III.

Mecholyl (acetyl-beta-methyl-choline chloride or bromide) was given to nine patients, Table IIIA, and only occasionally produced slight contractions without increase of tone. Doryl (carbamylocholine chloride) was given to ten patients and found more effective (Table IIIB). Excellent contractions were occasionally observed following 2.0 mg. of Doryl swallowed or placed under the tongue. In all, eight of the ten patients had contractions and only two had no effect. Significant side effects were not observed.

While Doryl was being studied, Machella, Hodges and Lorber<sup>13</sup> suggested that Urecholine (urethane of beta-methyl-choline chloride) might prove effective, as they had obtained good results in two patients. Effects produced by Urecholine are summarized in Table IIIC and the response of two patients shown in Figure 3. Administered subcutaneously to eight patients, it produced good contractions in each with increase of tone in four. Given orally or dissolved under the tongue, small doses (5 to 30 mg.) usually had no effect. Thirty milligrams under the tongue increased motility in three of seven patients. Restoration of contractions and increase of resting tone were most consistently produced by oral or sublingual administration of 40 to 50 mg. Side effects were insignificant; mild symptoms of flushing, sweating, and salivation occurred occasionally with these larger doses but were not troublesome.

#### DISCUSSION

It seems apparent that the changes of gastric motility after vagotomy in rabbits and dogs differ from those observed in man. Hypermotility was usually produced in these animals and hypomotility in man. Gastric retention, how-

TABLE 3.—*Effect of Mecholyl, Doryl and Urecholine on Gastric Motility in Ulcer Patients Treated by Vagotomy*

	Dose	No. of Tests	Tone		Contractions		Height of Contraction	Time of Onset (Min.)
			No Change	Increased	No Change	Restoration		
A. Mecholyl								
1. Subq.	10 mg. ....	2	2	0	0	2	0-2 cm.*	1-2
2. Orally	0.2 Gm. ....	7	7	0	5	2	0-2 cm.	10-15
B. Doryl								
1. Subq.	0.15 mg. ....	1	1	0	1	0	—	—
	0.25 mg. ....	1	1	0	0	1	0-2 cm.	20
2. Under Tongue	2.0 mg. ....	7	5	2	1	6	2-6 cm.	30-75
3. Orally	2.0 mg. ....	1	0	1	0	1	6 cm.	90
C. Urecholine								
1. Subq.	1.0 mg. ....	2	2	0	0	2	0-2 cm.	2-5
	2.0 mg. ....	1	1	0	0	1	2-4 cm.	10
	2.5 mg. ....	4	1	3	0	4	4-6 cm.	2-10
	5.0 mg. ....	1	0	1	0	1	0-2 cm.	4
2. Under Tongue	5.0 mg. ....	1	1	0	1	0	—	—
	10.0 mg. ....	3	3	0	2	1	0-2 cm.	50
	20.0 mg. ....	1	0	1	0	1	2-4 cm.	145
	30.0 mg. ....	7	7	0	4	3	2-4 cm.	60-120
	40.0 mg. ....	1	1	0	0	1	0-2 cm.	150
	50.0 mg. ....	2	0	2	0	2	2-4 cm.	150-210
3. Orally	10.0 mg. ....	1	1	0	1	0	—	—
	50.0 mg. ....	1	0	0	0	1	2-4 cm.	120

\*cm. of bromoform.

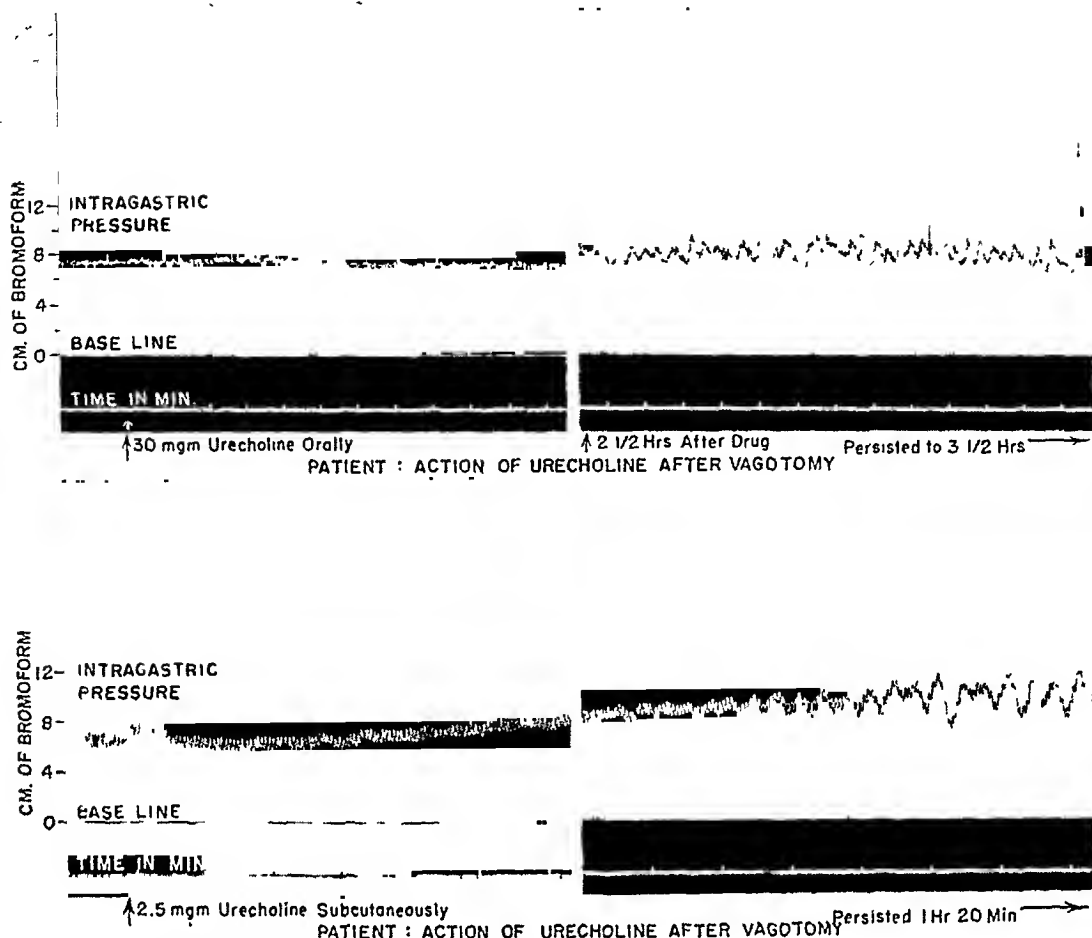


FIG. 3.—Restoration of fluctuations of intragastric pressure in 2 patients treated by vagotomy and then 3 weeks and 3 months later given urecholine orally (above) and subcutaneously (below).

ever, occurs in rabbits and dogs without scar tissue from ulcer and in patients with duodenal or gastric ulcer. Discussion of differences in motility, similarity in retention, and similarity in drug action will be presented separately.

Although development of hypermotility in animals after 12-48 hours made investigation of drug action difficult, it nevertheless represents a phenomenon, the explanation of which may have clinical significance. Ophuls<sup>14</sup> and Auer<sup>15</sup> first reported return of motility in rabbits after vagotomy and this has subsequently been confirmed by several observers. In our experiments return of motility in rabbits has been evidenced by contractions of excessively high amplitude occurring with abnormal rapidity.

Vanzant<sup>16</sup> recently reported changes of motility and secretions in dogs followed ten to 57 months after vagotomy. In seven of eight dogs, emptying time returned to normal and in one there was increased emptying. It is not clear whether she means initial emptying time or time of complete emptying. It is generally difficult in the literature to separate accounts of emptying time based upon initial emptying from those based upon complete emptying.

Regardless of the type of observation it is generally stated that some degree of recovery of motor activity occurs. Vanzant suggested that return of motility might be due to: (1) regeneration of the severed nerves, (2) assumption of



stimulatory function by splanchnic parasympathetic fibers or (3) spontaneous restoration by an intrinsic mechanism in the stomach. The first assumption was thought unlikely since sections of the stomachs showed degenerated nerve fibers. The second was thought not applicable since secretions and motility returned when both vagi and splanchnics were served. She therefore felt that the third explanation, restoration by intrinsic mechanism, was most likely.

It is evident from our observation and those of others that nerve regeneration could not explain return or recovery of motility within one or two days. Also, it was found in our acute experiments on previously vagotomized animals that cutting or stimulating the vagus nerves in the neck had no effect on gastric motility, thus establishing completeness of the transthoracic vagotomy and ruling out recovery by overlooked nerve fibers or regeneration. In these animals vagotomized for two weeks or more insulin produced cessation of motility for half an hour like that observed in normal rabbits. Subsequent restoration of motility, however, was equivalent to that before insulin and not to the hyperactive level seen in normal animals. It would appear therefore that the immediate action of insulin is inhibition of motility and that this action occurs whether the vagi are intact or absent. Also, it would appear that hypermotility occurring a half hour or more after insulin in normal rabbits does not recur after transthoracic or cervical vagotomy. Extravagal parasympathetic pathways if present apparently cannot mediate this hypermotile response.

The explanation of spontaneous restoration of motility in animals after both vagotomy and splanchnicectomy, by intrinsic mechanisms of the stomach rather than regeneration, or extravagal pathways may not apply to humans. It is still interesting to speculate that the difference observed in patients both in motility and response to insulin hypoglycemia might be related to presence or effectiveness of extravagal pathways.

A difference exists between animals and man that might be related to the different results of vagotomy on motility. Van Yzeren<sup>18</sup> in 1901 reported development of gastric ulcers in rabbits after vagotomy, and this was early confirmed by others.<sup>14, 15</sup> In man, after vagus section, gastric hypomotility occurs and persists for at least 2½ years as judged by 300 cc. balloon manometric methods. It is generally accepted that vagotomy causes healing of ulcers in patients. Therefore, after transthoracic vagotomy in rabbits, gastric hypermotility and occasionally ulcer formation occur, whereas after the same procedure in man, gastric hypomotility and healing of ulcer are produced.

Prolonged or excessive retention of gastric content and distention of the stomach occurred in rabbits. Efforts to empty completely the stomach by starvation, liquid diet, lavage, or gastrostomy usually failed. Retained food or secretion may have played a role in the hypermotility described.

Gastric retention also occurs in patients. This manifests itself clinically even though suction is continued four or five days and occurs as soon as light feedings are given. Delayed emptying is associated with decreased gastric motility and may not be the same in all patients. One explanation of retention

in patients after vagotomy is atony. Our measurements of resting intra-gastric pressure, however, show little change or increase of tone. A second explanation is that scarring about the ulcer may cause obstruction. Retention, however, is found in patients with or without ulcer. A third theoretical explanation of retention may be pylorospasm. A fourth more plausible explanation is derangement of the ejection cycle of the stomach. Normally, during digestion a peristaltic wave passes down through the antrum and separates a bolus of food from the main mass. The pylorus then relaxes and the bolus passes through. After vagotomy this "biting off" of a bolus does not occur as observed fluoroscopically, and the propulsive action of the diminished peristaltic waves mechanically fails to carry food through the pylorus. Since retention occurs in animals without ulcer and with hypermotility of an abnormal sort it would appear that pylorospasm or failure of the ejection cycle is an important factor causing obstruction, retention and dilatation.

If the explanation by faulty ejection cycle is correct, then stimulation of peristalsis by drugs during the postprandial period might produce satisfactory emptying. The studies reported show that subcutaneous injection of Doryl or Urecholine will produce contractions of amplitude and frequently equal to or greater than those seen preoperatively, as judged by intragastric balloon studies. Doryl or Urecholine dissolved under the tongue or given orally will cause similar contractions, although usually the onset is delayed. That Urecholine will cause increased peristalsis and prompt emptying of the stomach of vagotomy patients has been demonstrated fluoroscopically by Machella, Hodges and Lorber;<sup>13</sup> by Grimson and co-workers,<sup>7</sup> and by others.

Decreased or abnormal motility, therefore, seems to be the cause of retention, and faulty motility and retention can both be corrected by injection of drugs. Maintained treatment of vagotomized patients with retention by Urecholine however, although partially effective, has not eliminated necessity for occasional secondary drainage operations.

#### CONCLUSIONS

1. In rabbits, cervical or transthoracic vagotomy is followed by cessation of motility for 12-48 hours and subsequently by development of abnormal hypermotility and retention.
2. Insulin hypoglycemia produces arrest of motility followed by hypermotility. The hypermotility is promptly abolished by cervical vagotomy.
3. In rabbits during the 12-48 period of absent motility after cervical vagotomy, insulin hypoglycemia fails to restore motility.
4. During the subsequent period of hypermotility, several days after transthoracic vagotomy in rabbits, insulin abolishes motility for about half an hour following which there is restoration of motility like that before insulin.
5. During the first 12-48 hours after cervical vagotomy in rabbits, the choline derivatives and pilocarpine effectively restore contractions.

6. In ulcer patients following vagotomy decrease of amplitude of gastric contractions occur, as judged by 300 cc. balloon techniques but resting intragastric pressure usually slightly increases.

7. Doryl and Urecholine may restore amplitude and frequency of gastric contractions of vagotomized patients toward normal.

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# PURE SERUM ALBUMIN COMPARED WITH CITRATED PLASMA IN THE THERAPY OF CHRONIC HYPOALBUMINEMIA\*†‡

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WHEN PURE HUMAN ALBUMIN in 25 per cent solution became available for civilian use, we injected some of this material intravenously in patients with nutritional hypoalbuminemia. In our very first trials we found that it produced a significant elevation of the albumin concentration of the blood in contrast to the relative ineffectiveness of plasma transfusions. Several explanations were advanced, including the possibility that the pure albumin did not participate in the protein metabolic pool and therefore remained in the circulation longer than the intact albumin molecule present in the plasma. However, it seemed important to study this difference, particularly in relation to changes in plasma volume. We therefore set up a series of clinical experiments in which comparable injections were made in the same patient and variations carefully noted in the hematocrit, the fractional protein plasma concentration, blood and plasma volume and venous pressure. As a result of these studies we found that the pure albumin leads to a more lasting increase of albumin concentration because its effect on plasma volume is transient as compared with plasma. Other differences were also observed and will be described.

## PREVIOUS OBSERVATIONS

Concentrated solutions of pure human albumin were made possible because of the extensive research by E. J. Cohn and his collaborators<sup>9</sup> on the fractionation of human plasma which was collected and processed in large amounts by the American Red Cross during the past war. Considerable clinical investigation<sup>10, 12, 16, 17, 21, 22, 33, 34, 36, 37, 39, 40, 43</sup> has been carried out with this solution in patients, most of them suffering from shock or various types of hypoalbuminemia. These studies have shown that 25 Gm. of pure albumin is apparently equivalent in colloidal osmotic effect to 500 cc. of plasma and that each gram of albumin holds an average of approximately 18 cc. of water in the circulation. After injection most of the albumin was found to leave the circulation, but this was more pronounced in the chronic cases than in patients with

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\* The serum albumin used in this study was processed by the American National Red Cross from blood which it collected from voluntary donors.

This is one of a series of investigations on serum albumin being carried out with material supplied by the American National Red Cross. As soon as sufficient data become available to justify final conclusions concerning its therapeutic value, a full report to the medical profession on the use of serum albumin in medical practice will be published.

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shock. Attempts to correct hypoalbuminemia in nephrosis and cirrhosis were successful only when large amounts of albumin were injected.

Clinical experience with plasma has been fairly extensive, particularly as a blood substitute. It has also been used in patients with chronic hypoproteinemia, largely due to nephrosis. Pooled plasma as such or diluted with saline or glucose, as well as two to four times concentrated plasma (made up from the lyophilized or dry material) has been employed. Serum rather than plasma has also been used and with better effect, according to some observers.<sup>1</sup> In general the results were disappointing in patients suffering chronic depletion

TABLE I.—*Summary of Patients Studied*

Patient	Age	Sex	Diagnosis	Number of Injections		Reactions
				Albumin	Plasma	
1. A. D.	64	M	Ulcerative Colitis .....	1	—	See Text
				4	—	None
				—	1	Chills and fever
2. H. C.	69	M	Cirrhosis of Liver.....	2	—	None
				—	2	None
				—	—	None
3. L. B.	84	F	Carcinoma of Gallbladder.....	1	1	None
4. B. P.	60	M	Jejunal Ulcer.....	1	1	None
5. A. L.	43	M	Bronchiogenic Carcinoma .....	2	1	None
6. M. W.	36	M	Fracture of Spine.....	1	1*	None
7. W. A.	70	M	Carcinoma of Pancreas.....	1	1	None
8. J. C.	66	F	Carcinoma of Stomach.....	1	1*	None
9. E. R.	75	M	Carcinoma of Pancreas.....	1	—	None
10. G. H.	45	F	Non-tropical Sprue.....	—	1	Chills and fever
				3	—	None
11. B. P.	48	M	Cirrhosis of Liver.....	2	—	None
12. B. S.	71	M	Carcinoma of Pancreas.....	2	—	None
13. H. M.	71	M	Gastric Ulcer.....	1	—	None
14. P. B.	55	F	Stricture of Common Duct.....	1	—	None
15. E. N.	30	F	Carcinoma of Sigmoid.....	1	—	None
16. M. F.	54	F	Carcinoma of Pancreas.....	1	—	None
17. L. W.	66	M	Carcinoma of Stomach.....	1	—	None
18. C. L.	42	M	Arachnoiditis .....	1	—	None
19. M. M.	79	F	Intestinal Fistula.....	1	—	None
20. G. S.	71	M	Cirrhosis of Liver.....	—	1	Chills and fever
21. J. A.	66	M	Carcinoma of Hypopharynx.....	—	1	None
22. W. B.	56	M	Gastric Ulcer.....	—	1*	None
				29	13	

\* Pooled plasma from blood bank.

of plasma proteins, though success was claimed by some. Reactions following plasma and serum transfusions have been described as similar to those previously noted with blood. More recently pooled plasma has been found to transmit homologous jaundice even when lyophilized. This condition has not thus far been observed following the use of pure albumin prepared from pooled plasma; apparently the virus responsible for the disease is destroyed in the preparation of pure albumin.

#### METHODS AND PROCEDURES

Twenty-two patients were selected for study, as listed in Table I. They all were malnourished and showed a fall in the level of plasma albumin. The diagnoses included a variety of conditions, but none had nephrosis. Moreover, in only three, possibly four cases, was hepatic disease present and

responsible perhaps for some degree of impairment in albumin synthesis. Aside from these cases which also presented a history of food deprivation, it was assumed that the hypoalbuminemia was largely if not wholly of nutritional origin. With one exception, no patient showed any evidence of cardiac insufficiency.

All patients were observed for several days before study. Ample fluid intake was assured and vitamins given by either the oral or parenteral channel. Salt deficiencies were also corrected. In most cases whole blood had been injected to correct anemia.

The plasma used was prepared double strength by dissolving two units of lyophilized Red Cross plasma with one unit of distilled water. This made a volume of 600 cc. which was injected within 30 to 40 minutes. In three patients (Table 1) comparable amounts of pooled (unconcentrated) plasma from the Barnes Hospital blood bank were used. The findings were no different from those with the lyophilized plasma.

The 25 per cent albumin solution was injected without dilution. It had special physical and chemical properties, described in detail by Cohn and his co-workers.<sup>5, 6, 9, 29, 30, 31, 42</sup> First of all it was salt-poor, containing but 0.2 Gm. of sodium as sodium acetyltryptophane per 100 cc. of the 25 per cent solution. It also contained 0.1 molal isoleucine. These not only rendered the solution isotonic, heat stable (so that sterilization for 10 hours at 60° Centigrade could be carried out without need for preservatives), but also completed its essential amino acid composition (so that rat growth could be maintained on a diet containing no other source of nitrogen). Its low sodium content is to be contrasted with that in 500 cc. of plasma, which contains over ten times as much (2.1 Gm.)<sup>31</sup>

In nine patients both pure albumin solution and plasma were injected, the amount of albumin being the same in each case. In ten cases albumin only was given. The remaining three cases received plasma alone. Several days were allowed to elapse between repeated injections.

*Collection of Blood.* Previous to each injection a sample of heparinized blood was removed from the antecubital vein without stasis, the patient having been in the supine position. The importance of this position has been indicated by several observers.<sup>27, 35</sup> Successive samples were withdrawn five minutes after the end of the injection and thereafter at intervals of 1, 3, 6 and 24 hours. The red cells were separated from the plasma by transferring a portion of the blood to an 8 mm. diameter hematocrit tube and centrifuging at a rate of 3000 revolutions per minute for 40 minutes. The hematocrit value was recorded and the plasma carefully removed. Total and fractional protein determinations were made by the colorimetric method of Weichselbaum<sup>41</sup> which provides a direct measure of the amount of protein in the samples by the intensity of the color produced by a copper tartrate reagent. This biuret method was compared with the traditional nitrogen determinations (Kjeldahl) and excellent checks were obtained. As a further check

albumin by means of heat and acetic acid test and trichloroacetic acid precipitation.

### FINDINGS

The changes in the concentration of albumin following both the injection of 25 per cent pure human albumin and of plasma were plotted as a scatter

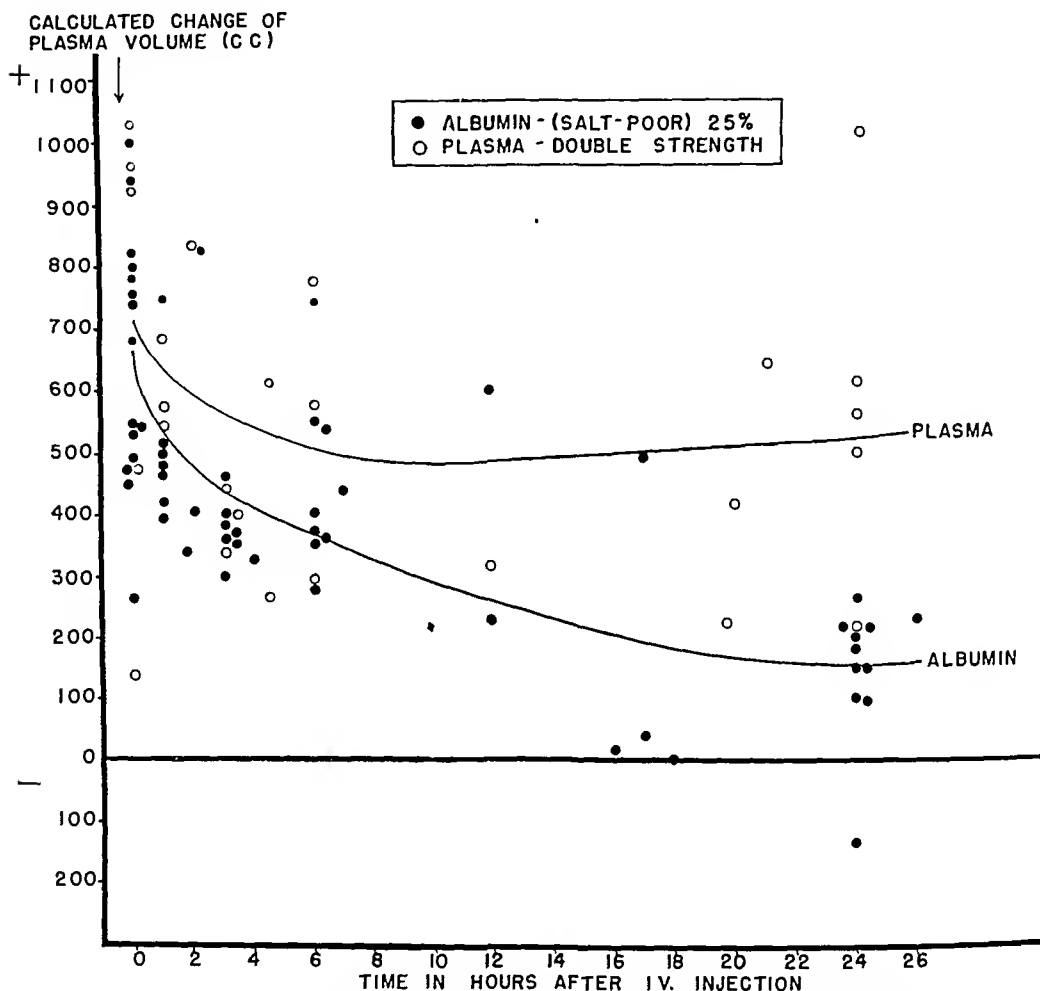


FIG. 2. CHANGES IN PLASMA VOLUME.—Each point represents a determination showing changes in plasma volume as calculated from formulas 1 and 2 (see text) following the injection of a 25% salt-poor human albumin injection and of double strength plasma. The two curves were plotted from mean values in each group. Statistical analyses of the curves show a significant difference in the values at 24 hours. Note the rapid return to the preinjection level in the case of pure albumin injection, in contrast to its more sustained level (average  $+500$  cc.) in the case of plasma transfusions.

diagram in Figure 1, and a curve, representing the mean change, calculated from these data. It will be obvious on consulting this figure that the initial rise in the concentration of plasma albumin which followed the injection in each case fell fairly rapidly, but that it returned to the initial level only in the case of the plasma injections.

In Figure 2 is a similar scatter diagram recording the changes in the plasma volume in the two groups of injections. Here it will be noted that

the initial increase in the plasma volume produced by each injection also fell during the subsequent 24 hours, but that the fall had produced a return to the initial level in case of the pure albumin, whereas with plasma there was still a significant increase at that time.

These differences are strikingly shown in Figure 3, which records the findings in a single typical case in which successive injections of albumin and plasma were given. Here it can be seen that the albumin concentration 24 hours after the injection of 25 per cent albumin solution is significantly higher

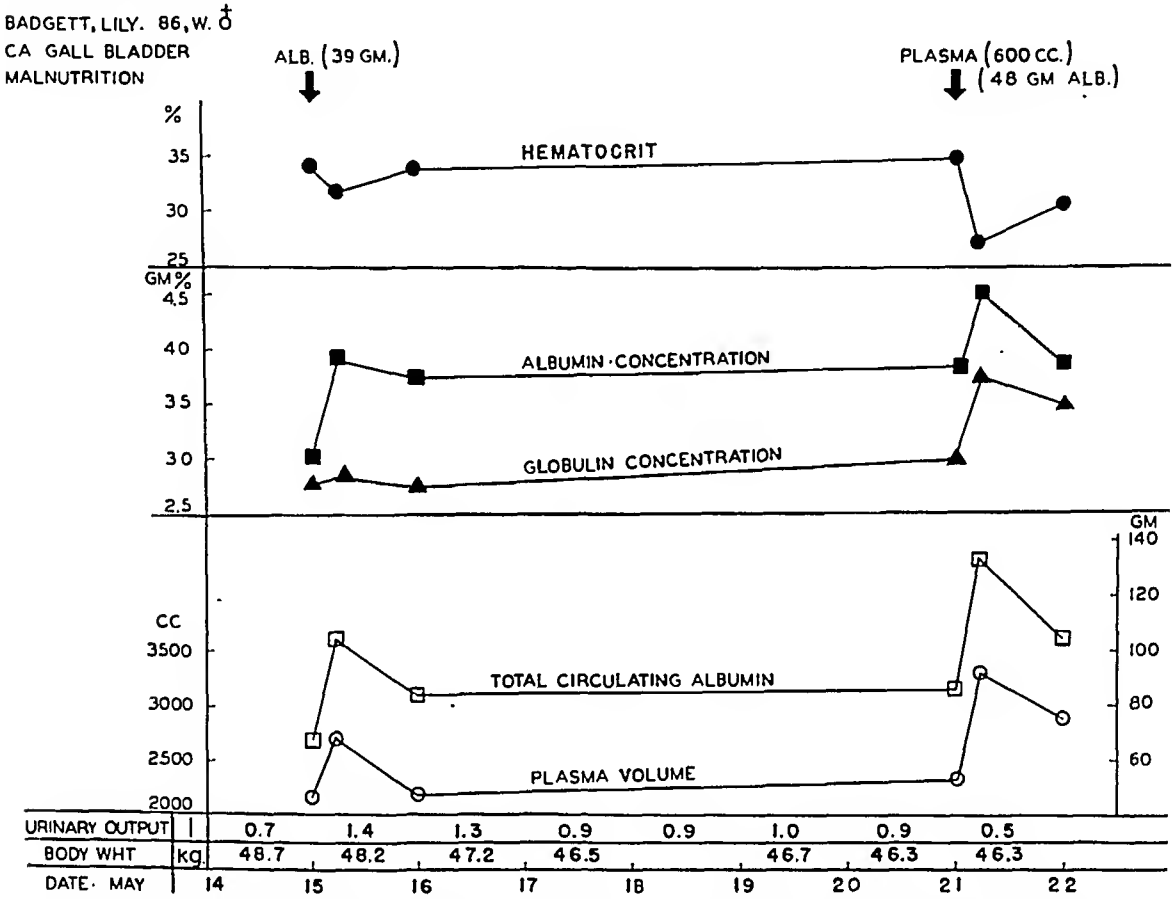


FIG. 3.—Observations made on a patient receiving both salt-poor albumin and double strength plasma at an interval of 6 days. Note the similarity in total circulating albumin. Note, however, that plasma produced a greater increase in plasma volume at 24 hours with no change in the concentration of albumin in contrast to the effect of the pure albumin solution which resulted in no change in plasma volume but a sustained increase in the concentration of albumin. Note also that the albumin produced a greater diuresis and a fall in body weight compared to the plasma.

than that following the injection of double strength plasma containing larger amounts of albumin. That this is the result of a more sustained increase in the plasma volume following plasma injection than that following albumin injection is likewise apparent, the changes in total circulating albumin being approximately equal.

That there was no change in the size of the red cell during our study is shown by the similarity of the curves in Figure 4. These curves record, in a typical case, the rate of disappearance of injected albumin (in per cent) as calculated from changes in both hematocrit and hemoglobin concentration



following injection. Moreover, no significant change was found in the mean corpuscular volume, mean corpuscular hemoglobin, or mean corpuscular hemoglobin concentration of the red blood cells of other patients receiving either concentrated human albumin or double strength plasma.

Of incidental interest is the behavior of albumin following repeated injections. In Figure 5 is recorded the disappearance curve of albumin following successive injections at intervals of several days in the case of both 25 per cent albumin solution and double strength plasma. The curves are based on the

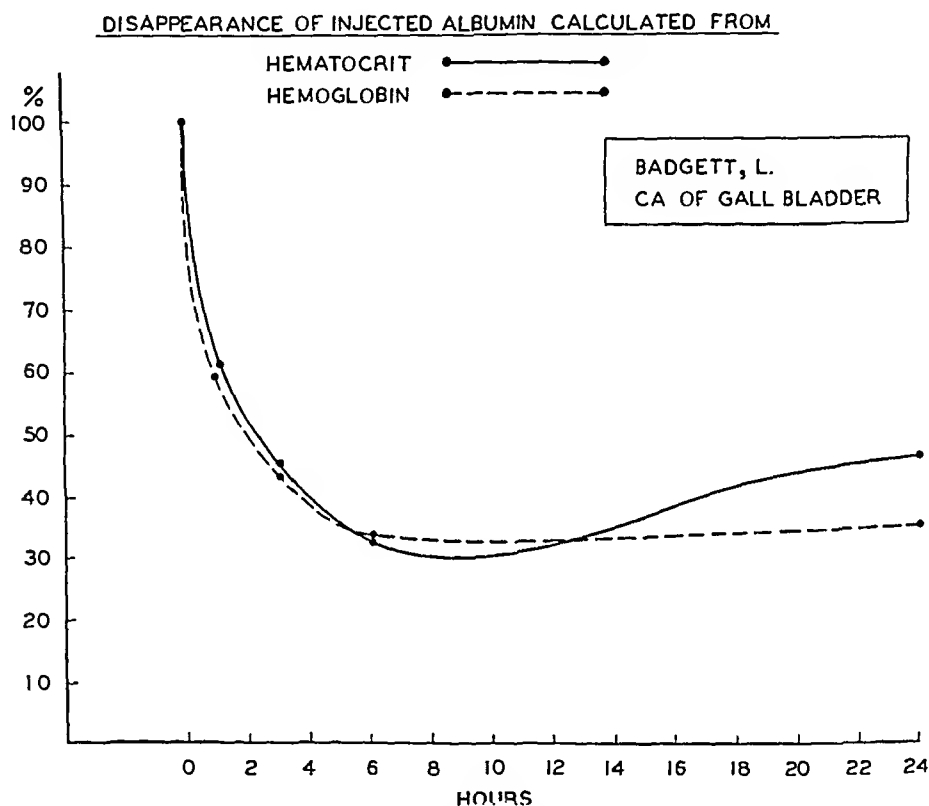


FIG. 4.—Disappearance curves of injected albumin as calculated from formulas 1 and 2 (see text) based upon both the hematocrit and hemoglobin measurements. Note that both curves are superimposable, thus showing that the red cell size was unchanged.

changes in the total circulating albumin calculated from its concentration and plasma volume. Apparently there is a greater retention of albumin in the blood as successive injections are given, either as double strength plasma or pure albumin.

*Reactions.* There was no significant change in pulse rate to respiratory rate in the absence of any reaction to the injected solution. However, there was a slight tendency toward an increase in pulse pressure in most cases. Increases in venous pressure were considered to be significant of an untoward effect. During five albumin injections the venous pressure was measured and only once was there an increase (from 100 to 230 mm. of isotonic saline). It was during an acute phase of the patient's illness when there was evidence of

cardiac failure. Subsequently albumin injections produced no increase in venous pressure in this patient. By contrast, in all six plasma transfusions in which venous pressure was measured, increases were noted. In three cases the pressure rose to 135, 140 and 152 mm. of isotonic saline. In the other cases severe pyrogenic reactions occurred and in them the pressure rose to 200, 300 and 310. In the majority of the cases in which the venous pressure rose during or after injection of either solution there was a slight further increase in venous

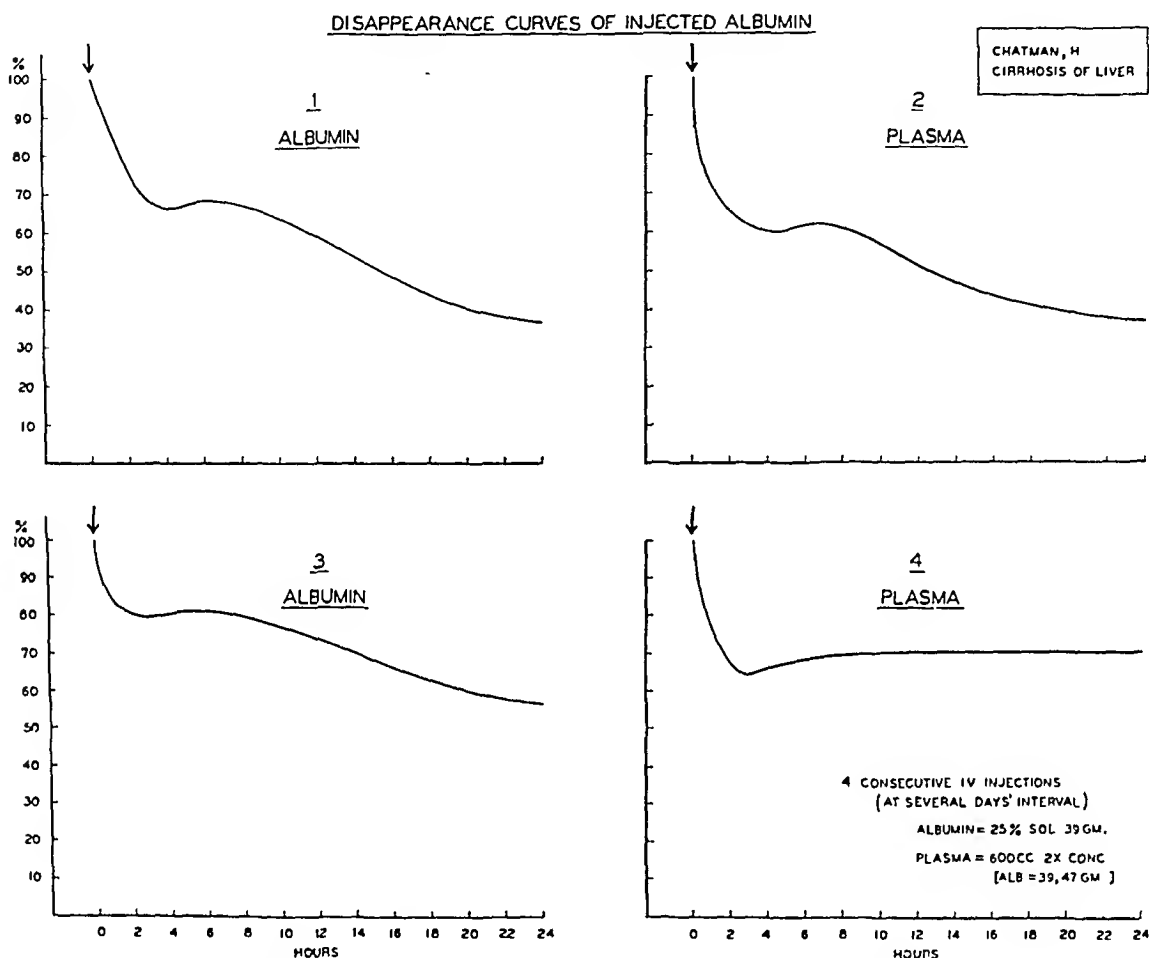


FIG. 5.—Disappearance curves of injected albumin following alternate infusions of a pure salt-poor albumin solution and of double strength plasma at several days interval, as calculated from formulas 1 and 2 (see text). Note that the disappearance rate diminishes with each successive injection.

pressure with feeling of pressure in the right upper quadrant of the abdomen.

Pyrogenic reactions were seen in three of the 13 plasma injections, none in the 29 injections of pure albumin. (Table I.) The reaction following plasma in one case was severe, with sudden dyspnea, orthopnea, pain in the retrosternal region and epigastrium, nausea and vomiting, cold, clammy skin, marked fall in arterial blood pressure, tachycardia, distention of the neck veins and increase in venous pressure from 80 mm. of isotonic saline to 300 mm. The hematocrit rose from 38.1 per cent to 42.9 per cent and plasma albumin concentration from 2.90 Gm. per cent to 3.65 Gm. per cent, plasma globulin concentration from 2.55 Gm. per cent to 3.50 Gm. per cent, while the whole blood volume as deter-

mined by the radioactive phosphorus technic, fell from 4470 cc. to 4060 cc., the decrease being entirely in the plasma compartment, (within the error of the method) which decreased from 2760 cc. to 2280 cc. In this patient, therefore, not only did the 285 cc. of injected plasma disappear from the circulation, but also an additional 480 cc. of the original plasma volume. In five other patients we also observed an increase in the hematocrit following plasma infusion, even though some of them exhibited no clinical evidence of reaction. Freeman and Wallace<sup>13</sup> found similar clinical symptoms and signs as well as a rise in the venous hematocrit of unanesthetized dogs given four times concentrated serum rapidly (0.8 cc./kg./min.). Harkins, Boak and Brush<sup>14</sup> made the same observation in dogs following infusion of four times concentrated plasma, but did not find this to be true in a small number of splenectomized dogs. Brennan<sup>7</sup> noted an increase in the red blood cell count in acutely anemic neurosurgical patients following the injection of half normal plasma. Neither we nor any other investigators have observed similar findings of a decrease in plasma volume following the injection of purified albumin solution.

Proteinuria was not detected in any cases following the injection of either salt-poor human albumin or concentrated plasma.

From the data on plasma volume it was calculated that there was an average increase of 13.7 cc. per Gm. of albumin immediately following the injection of the 25 per cent solution. The comparable increase in plasma volume immediately following the injection of double strength plasma was 22.7 cc. This increase in plasma volume was greater immediately after infusion than at any other time in almost all cases.

In all but one of the patients with edema, a copious diuresis with weight loss and obvious diminution of edema occurred following the injection of the pure albumin solution. Red Cross plasma was not nearly as effective. (See Fig. 3.) Diuresis always occurred within 48 hours of the time of injection and was most marked in the first 24 hours. However, one patient with cirrhosis of the liver with ascites and minimal scrotal edema continued to gain weight and his ascites worsened, in spite of a very significant diuresis following two 50-Gm. injections of salt-poor albumin.

#### COMMENT

From the present observations it would seem justified to infer that a 25 per cent solution of salt-poor albumin is far superior to plasma in the treatment of chronic hypoalbuminemia of nutritional origin. This inference is based first on the bedside observations. Not only did the effect on diuresis seem better, but the pure albumin produced no pyrogenic reactions and no increases in venous pressure, in contrast to the effect of plasma.

The greater plasma-volume-increasing effect of plasma may be advantageous in acute conditions. In chronic states it would seem that this is less important than the concentration of albumin itself, which is increased more effectively by the pure albumin solution. By increasing colloidal osmotic pres-

sure, this should be more useful in nutritional edema and this was borne out by our bedside observations.

One may speculate as to the reason plasma volume is increased to a greater extent and over a longer period of time following the injection of plasma than after injection of an equivalent amount of albumin as salt-poor albumin (25 per cent). Some of the difference may be due to the greater volume of the plasma injected, but most is probably due to its greater sodium content, both as chloride and citrate. Further study with pure albumin diluted to the same concentration with or without added salt would probably answer this question.

Variations in the size of the red blood cells following infusion of concentrated human serum albumin solution seem to have received little notice. Metcalff,<sup>25</sup> using the same measurements we have used, demonstrated a decrease in the size of the red blood cells of dogs given concentrated serum as infusions. Harkins, Boak and Brush,<sup>14</sup> and Ashworth, Muirhead and Hill,<sup>2</sup> using the same indices, failed to demonstrate any change in the size of the dog's red blood cells following the injection of normal or hypertonic citrated or defibrinated plasma. Our findings in the human agree with the latter.

The disappearance from the circulation of injected albumin either as plasma or as concentrated albumin solution is of considerable interest and importance. Metcalff<sup>25</sup> concluded from studies on dogs receiving infusions of normal and concentrated serum or plasma that the rate of disappearance of protein from the circulation is logarithmic and therefore related to the total amount of protein in the circulation. Using labeled plasma protein in experimental animals, Schoenheimer et al indicated a "half-life" of plasma protein of about 14 days, whereas Bale and others, using similar technic, found that 50 per cent of the injected protein had disappeared from the circulation within 30 hours and 75 per cent within 6 days.<sup>4</sup> These authors did not find the rate of disappearance of injected protein to be logarithmic.

There is some suggestion from our data, as exemplified in Figure 5, that there is greater retention of albumin in the blood stream with successive injections given several days apart. There is no evidence that the albumin in the salt-poor albumin solution is any better in this respect than plasma. It may indicate that the extravascular sites become saturated on repeated injection. We have been unable to find any correlation between the severity of the malnutrition and hypoproteinemia and the retention of albumin in the circulation.

The initial plasma volume per kilogram of body weight noted in the present study was slightly lower than the average normal plasma volume reported in the literature and somewhat lower than the average normal plasma volume determined in this laboratory by means of the radioactive phosphorus method. The red cell volume and the whole blood volume were likewise lower. Two cases of cirrhosis of the liver had somewhat elevated plasma volume, the red cell volume being low and the whole blood volume normal or slightly elevated. This low value would be even more striking if the plasma volume, red cell volume and whole blood volume were calculated on the basis of the patient's

normal body weight before illness because all of these patients, even those in whom edema was present, had lost considerable weight. The decreased blood and plasma volume we found in patients with malnutrition and hypoproteinemia is in agreement with the results obtained by Walters, Rassiter and Lehmann<sup>38</sup> in repatriated prisoners of war. These authors used the dye method for the determination of plasma volume. With dietary treatment over several weeks they found the plasma and red cell volume to return to normal levels. On the other hand, Denz,<sup>11</sup> in a similar though less complete study, found the plasma volume to be increased in prisoners of war before treatment and to fall as their condition improved. Henschel et al<sup>15</sup> were in agreement with Denz. We found the plasma volume to increase with successive injections of both salt-poor albumin or concentrated plasma. There was no significant change in the red cell volume.

The figure calculated herein (13.7 cc.) for the increase in plasma volume per Gm. of injected albumin (as pure salt-poor albumin) is considerably lower than either the theoretical volume of 18 cc. per Gm.<sup>31</sup> or the values reported in previous clinical studies in man.<sup>10, 17, 21, 22, 33, 34, 36, 37, 40, 43, 39</sup> This discrepancy may well be explained by the fact that, unlike the method used herein, all of the clinical studies mentioned employed the dye method for determination of plasma volume. Use of the dye would be most likely to be misleading in patients in shock or patients with cirrhosis or nephritis. The larger figure calculated herein (22.7 cc.) for the increase in plasma volume per Gm. of albumin injected (as double strength plasma) may be due to the additional salt and protein present. Further studies would undoubtedly reveal the true explanation.

The effectiveness of salt-poor albumin in causing diuresis in cases of cirrhosis and nephrosis has been demonstrated by Thorn et al.<sup>36, 37</sup> It is likewise well known that plasma transfusions are much less effective in these patients and Leutscher<sup>22</sup> obtained little benefit from one injection of concentrated human albumin solution containing sodium chloride in patients with nephritis. We have found salt-poor human albumin to be much more effective than concentrated plasma in inducing diuresis with weight loss and relief of edema in patients receiving alternate injections of the two solutions containing equivalent amounts of albumin. The sodium content of the concentrated plasma may well explain this difference. That the sodium citrate may be responsible is indicated by the beneficial effect on nephrosis in children with injections of concentrated serum.<sup>1</sup>

The absence of untoward reactions following the injection of salt-poor human albumin is noteworthy, especially in contrast to frequency of reaction to concentrated Red Cross plasma. Homologous jaundice was not seen by us, but has been observed by others with plasma and must be counted as a disadvantage to the use of plasma not shared by pure albumin. Our observations on venous pressure, which usually increased significantly during plasma infusion and rarely during or immediately after albumin injection, must also be listed

as a mark of superiority of the latter over the former. This difference is probably due to the greater volume of fluid injected as well as its content of sodium chloride and citrate, which results in a greater increase in plasma volume.

The data presented herein have no bearing on the question of utilization of intravenously injected albumin. From the data obtained it is clear that albumin leaves the circulation just as rapidly when given as a salt-poor 25 per cent solution or as double strength plasma. Thus the metabolic behavior of the albumin in each case is probably the same. The superiority of the pure albumin in maintaining an elevated albumin concentration, therefore, is probably a temporary one, lasting for at least 24 hours. Our data gives no information in regard to its behavior after this period. Nevertheless, an effect lasting even for such a short period of time is of significance in the practical treatment of patients suffering a nutritional depletion of plasma albumin.

#### SUMMARY

1. Comparable injections of twice concentrated plasma and of 25 per cent salt-poor human albumin were studied in 22 patients with various diseases having in common malnutrition and hypoalbuminemia.

2. Both solutions caused an immediate and similar increase in albumin concentration, in total circulating albumin and in plasma volume. However, significant differences were apparent within 24 hours. The concentration of albumin was more sustained with the solution of pure albumin than with plasma. This was due to the more sustained elevation of plasma volume produced by plasma. There was no significant difference in the increase of total circulating albumin following injection of either solution.

3. Pure albumin produced no increase in venous pressure whereas plasma did, particularly when a reaction occurred. No reactions occurred with albumin in contrast to their frequency with plasma.

4. There was no change in the size of the red blood cells following injection of either albumin or plasma.

5. The pure albumin solution was more effective than plasma in inducing diuresis with weight loss and relief of edema.

6. Solutions of 25 per cent salt-poor albumin would seem to be far superior to plasma in the treatment of nutritional hypoalbuminemia.

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# STRANGULATED DIAPHRAGMATIC HERNIA \*

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STRANGULATION HAS BEEN RECOGNIZED to be one of the most serious complications of the diaphragmatic hernia since Pare's<sup>47</sup> description of a case found at necropsy in 1564. Occasional cases of strangulated diaphragmatic hernia have been reported in the earlier literature, but prior to the widespread employment of roentgenography, the condition was seldom correctly diagnosed. In this paper strangulation is defined as the arrest of circulation due to compression. Compilation of reports from 1798 to the present reveals that the clinical picture follows a relatively stereotyped pattern which has not previously received adequate attention. In view of the fact that early surgical intervention alone can avert a fatal outcome, a discussion of this condition as a clinical and diagnostic entity seems warranted.

Our attention has been drawn to this condition by the observation of two cases within the past year, the first of which presented a clinical picture so atypical in our experience that a 24-hour delay before operation occurred, with subsequent death of the patient. Aroused by this incident to review the literature, we were able to collect 39 cases of strangulated diaphragmatic hernia and in all of them there was a strikingly repetitious symptomology. These cases are summarized here, together with four additional from the Cincinnati General Hospital (Table I).

Case 1.—A. G., colored male age 33, was admitted to the Cincinnati General Hospital April 13, 1947, with a history of cramp-like, non-radiating, epigastric and left upper quadrant pain for 23 hours. This pain was persistent, and had been accompanied in the ten hours previous to admission by vomiting of food without blood. From the time of onset there had been complete constipation. Two months previously he had been admitted to the surgical service with two stab wounds of the thorax; one a sucking wound of the right posterior thorax and the other in the left fifth interspace in the axillary line. There had been some doubt as to whether the latter had penetrated the pleura. A right hemopneumothorax developed after wound closure, but convalescence was otherwise uneventful, and he had returned to heavy labor.

Physical examination revealed a well nourished colored male who appeared acutely ill. Left diaphragmatic dullness could be percussed at the sixth interspace, and did not move on deep respiration. The abdomen was not distended; peristalsis was generally hypoactive. There was mild upper and left lower quadrant tenderness without spasm. No release tenderness was noted. There was an indefinite, vertically placed, fairly firm mass in the left lower abdomen, which was slightly tender and dull on percussion. Rectal examination was negative. Roentgenograms showed "high left diaphragm" and displacement of the heart to the right; films of the abdomen showed air in the large and small bowel with evidence of ileus (Fig. 1a). Barium enema revealed mesial and upward displacement of the sigmoid colon, but good filling and no evidence of obstruction (Fig. 1b). Transient "gurgling noises" in the left thorax were noticed by one observer. A diagnosis of left subphrenic abscess or delayed ruptured spleen was considered.

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TABLE I.—*Strangulated Diaphragmatic Herniae*

Reporter and Date	Etiology	Type of Injury	Interval to Attack	Correctly Diagnosed	Hernial Contents	Operation Performed	Survival
(1) Cooper 1798 .....	congenit.	—	—	no	trans. colon, omentum	no	no
(2) Boyle 1812 .....	traumatic	stab	11 mos.	no	trans. colon, small intest., oment.	no	no
(3) Gretham 1832 .....	traumatic	stab	?	no	trans. colon, stomach, omentum	no	no
(4) Reid 1840 .....	traumatic	stab	15 mos.	no	trans. colon, omentum	no	no
(5) Thompson 1847 .....	traumatic	gsw	1 year	no	splenic flexure	no	no
(6) Maiden 1869 .....	traumatic	stab	1 year	no	splenic flexure, omentum	no	no
(7) Hull 1874 .....	traumatic	stab	1 year	no	transverse colon	no	no
(8) Woodworth 1874 .....	traumatic	indirect	10 days	no	small intestine, colon, omentum	no	no
(9) Ord 1887 .....	?	—	—	no	splenic flexure, omentum	no	no
(10) Farwell 1888 .....	traumatic	indirect	16 years	no	stomach, small intestine	no	no
(11) McCloskey 1895 .....	congenit.	—	—	no	stomach, sm. intest., spleen, colon, omentum	no	no
(12) Mixter 1900 .....	?	—	—	no	colon, omentum	yes	no
(13) Home 1900 .....	traumatic	gsw	4½ mos.	no	transverse colon, omentum	yes	no
(14) Hawkes 1917 .....	traumatic	stab	9 mos.	no	splenic flexure, small int., oment.	yes	yes
(15) Symonds 1917 .....	traumatic	gsw	?	yes	stomach, tr. colon, sm. int., oment.	yes	no
(16) Warren 1919 I. ....	traumatic	indirect	3 years	no	stomach, small intestine	yes	no
II	traumatic	gsw	3 years	no	stomach, small intestine	yes	yes
III	traumatic	gsw	?	yes	stomach, small intest., tr. colon	yes	no
(17) Bryan 1921 .....	traumatic	indirect	10 days	no	stomach, transverse colon, omentum	no	no
(18) Waxman 1922 .....	traumatic	gsw	2 years	no	splenic flexure	yes	no
(19) Crook 1923 .....	traumatic	stab	12 years	no	splenic flexure, tr. colon, oment.	yes	yes
(20) Slater & McKenzie 1923. ....	traumatic	gsw	4 years	no	stomach, transverse colon	yes	no
(21) Stone 1923 .....	congenit.	—	—	yes	splenic flexure	yes	yes
(22) Ellis 1928 .....	?	—	—	yes	transverse colon, omentum	yes	no
(23) Gibson 1929 I. ....	traumatic	stab	3 years	yes	colon	yes	yes
II	traumatic	indirect	?	yes	stomach, transverse colon	no	no
III	traumatic	indirect	1 day	yes	stomach	yes	yes
(24) Russell 1930 .....	traumatic	gsw	?	yes	stomach	yes	no
(25) Johnson & Bowen (1932) ...	congenit.	—	—	yes	small intestine, ascending and transverse colon, omentum	yes	yes
(26) Wright 1935 .....	traumatic	indirect	?	no	stomach, spleen, omentum	yes	no
(27) Mast and McDonough 1937..	traumatic	gsw	8 mos.	yes	stomach and small intestine	no	no
(28) Swinney 1942 .....	traumatic	stab	6 weeks	yes	stomach	yes	yes
(29) Deaner, McMenemy, Smith 1943 .....	?	—	—	no	stomach and omentum	no	no
(30) Jamieson 1943 .....	traumatic	stab	1 year	yes	stomach and omentum	yes	yes
(31) Gardiner .....	?	—	—	yes	stomach	yes	yes
(32) Pfahl, Lund, 1944 .....	traumatic	stab	18 mos.	no	transverse colon	no	no
(33) Mackey, Bingham 1945 I. ....	traumatic	gsw	6 mos.	no	splenic flexure, transverse colon	yes	no
II	traumatic	gsw	3 years	yes	splenic flexure, transverse colon	cecostomy	no
III	traumatic	gsw	6 mos.	yes	stomach and omentum	yes	yes
Cases from the Cincinnati General Hospital							
G. H. 1933 .....	traumatic	indirect	10 weeks	yes	transverse colon and omentum	yes	yes
E. L. 1945 .....	traumatic	gsw	18 mos.	yes	transverse and descending colon, omentum	yes	yes
A. G. 1947 .....	traumatic	stab	2 mos.	no	stomach, omentum	yes	no
W. H. 1947 .....	traumatic	stab	7 years	yes	transverse and descending colon, omentum	yes	yes

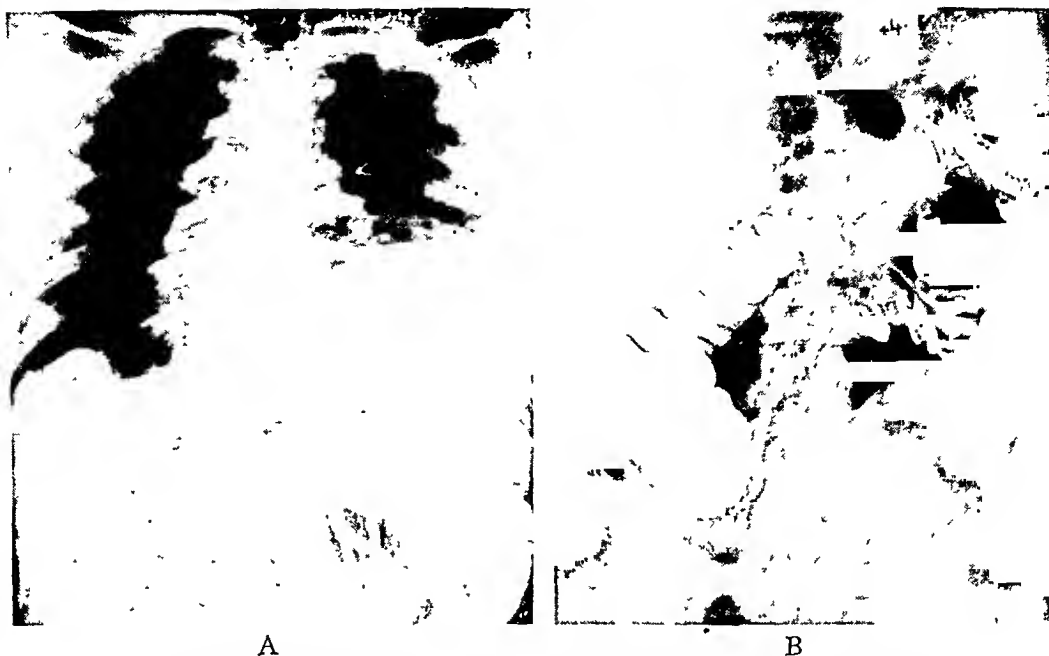


FIG. 1.—Case IA. Roentgenogram showing the heart displaced to the right and what appears to be a high left diaphragm, but actually is stomach herniated into the left thorax.

B. Roentgenogram following barium enema revealing satisfactory filling of the large bowel.

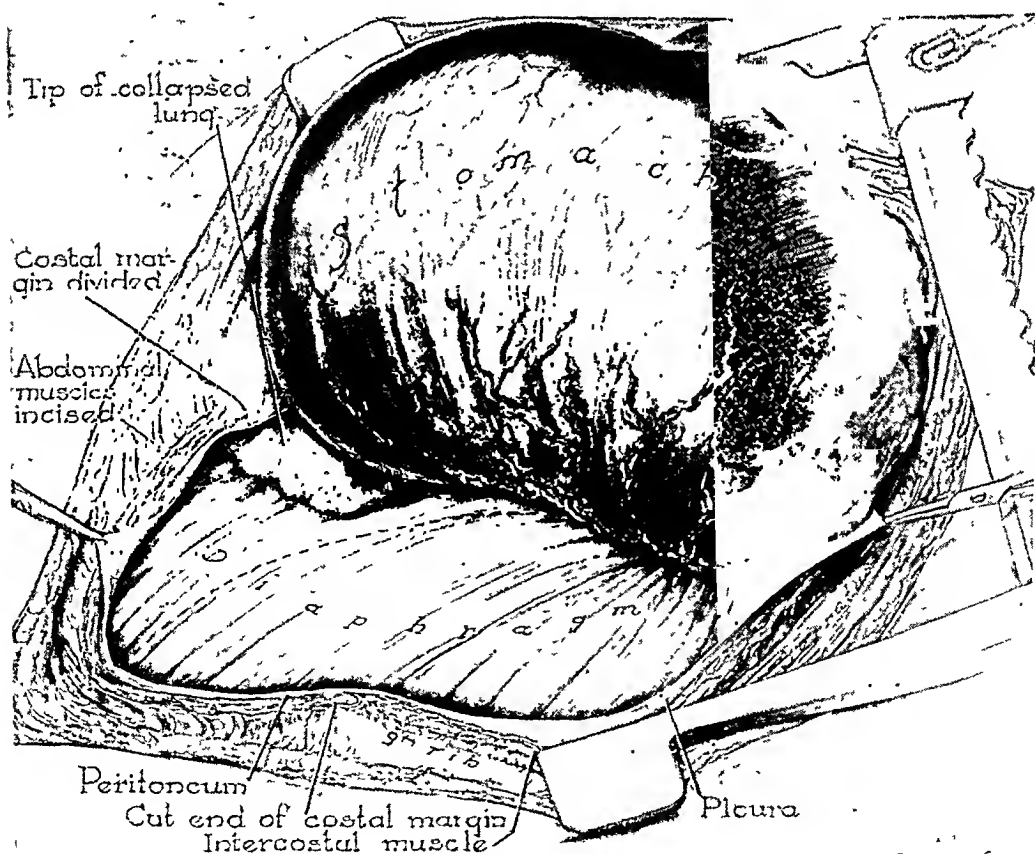


FIG. 2.—Case I. Drawing illustrating conditions found at operation. Note the greatly dilated gangrenous stomach, filling a large portion of the left thorax. The original incision was a thoracic one in the eighth interspace, subsequently prolonged across the costal margin into the abdomen.

## STRANGULATED DIAPHRAGMATIC HERNIA

Several hours after admission he suddenly manifested signs of shock with peripheral circulatory collapse. At this time the left thorax had become dull to percussion up to the second interspace. Thoracentesis produced 550 cc. of fluid which resembled pure blood and had a RBC of 1.9 million.

Transfusion of 500 cc. of whole blood was followed by a rise in blood pressure. During the next few hours an additional 1,000 cc. of bloody fluid were removed from the left thorax. The following morning he manifested signs of increasing shock despite continuous blood transfusion. Repeat chest film showed increased mediastinal shift to

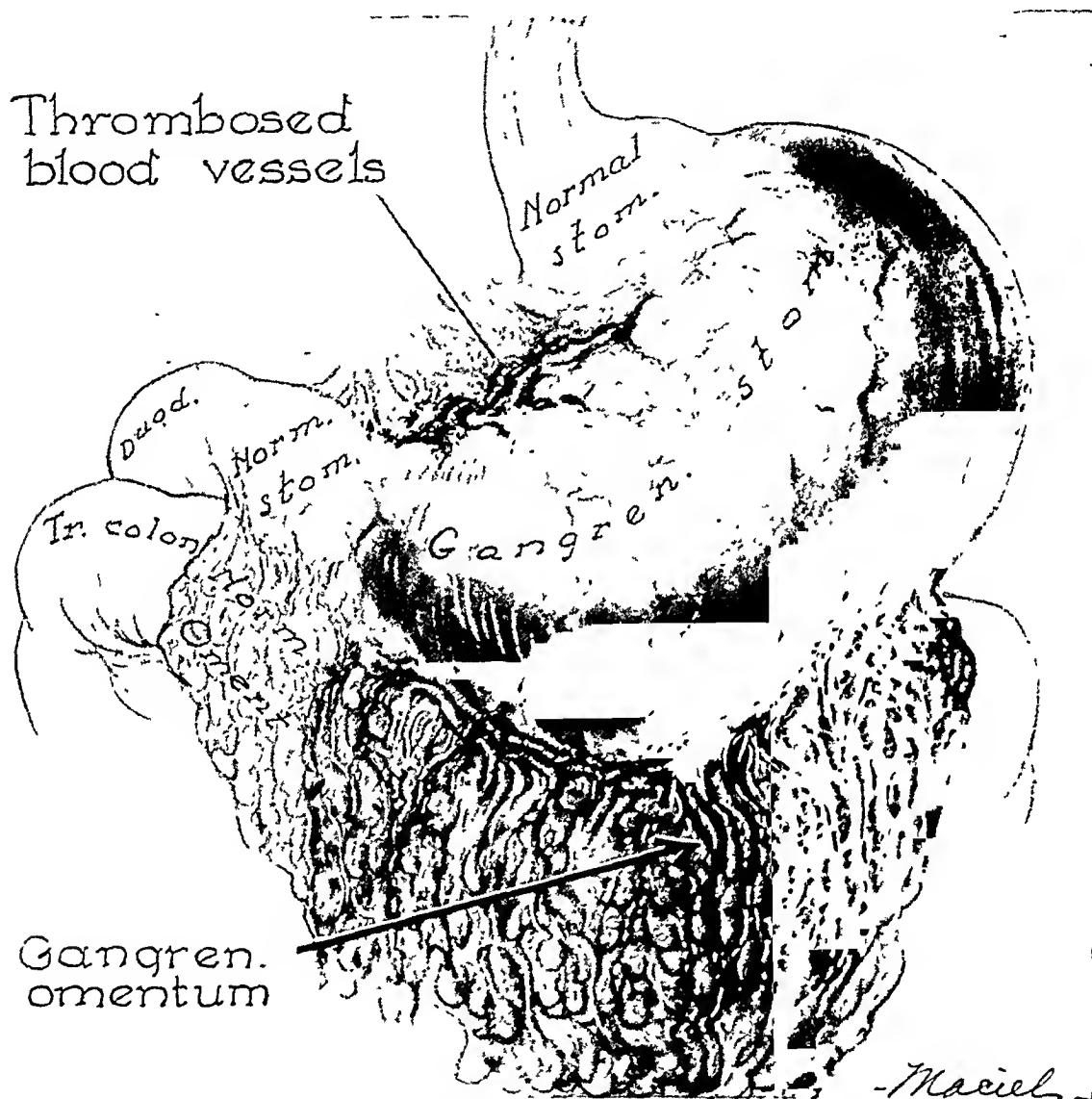


FIG. 3.—Case 1. The hernial orifice was so small that it precluded reduction of the stomach. Accordingly, the diaphragm was incised beginning at the costal margin and a clamp introduced through the hernial defect, in order that the remainder of the diaphragm could be safely divided, thus permitting adequate exposure of the stomach for reduction.

the right; unchanged position of the "high diaphragm," and increased amount of fluid in the left thorax.

At exploration, through a combined thoraco-abdominal incision, the stomach and spleen were found to be herniated through a rent in the diaphragm and the former to be entirely gangrenous save for a small segment of the greater curvature at the cardiac end (Fig. 2, 3). The entire omentum was gangrenous (Fig. 4). There was an estimated 1,000 cc. of bloody fluid in the pleural cavity. The gangrenous portion of the stomach

was resected and a post-colic Polya type gastro-jejunostomy was performed, only a small portion of the cardiac end of the stomach remaining as a pouch. The spleen and all of the omentum were removed.

Postoperatively there was evidence of improvement for 12 hours; however respirations became shallow and rapid, cyanosis could not be overcome by oxygenation or bronchial aspiration, and the patient expired 3 hours after operation.

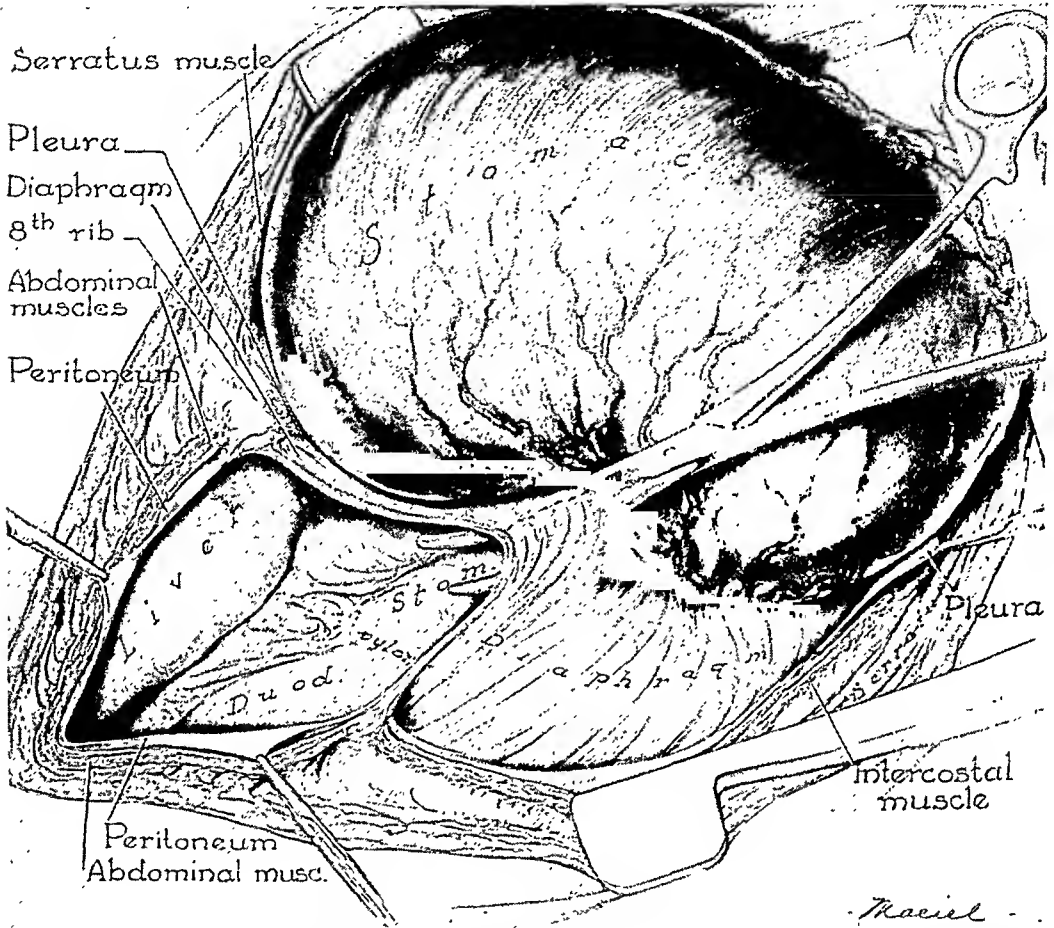


FIG. 4.—Case 1. Diagrammatic illustration indicating the extent of the gangrenous area of the stomach. Note the thrombosed vessels along both curvatures and the gangrene of the omentum.

An autopsy was performed and no immediate cause of death was discovered. There were 200 cc. of bloody fluid in the left thorax, the anastomosis was intact though there was a local area of gangrenous mucosa on the anterior wall of the stomach pouch, the heart appeared normal, and the lungs were crepitant. The mass in the lower left quadrant was a prolapsed kidney.

#### COMMENT

The correct diagnosis in the case was missed entirely and was not made until the thorax had been opened at operation. In retrospect the confusing features were: (1) the "high diaphragm" which was in reality the herniated stomach whose appearance on the roentgenogram accurately simulated that of an elevated diaphragm, (2) the absence of abdominal distention which was due to the stomach alone, unaccompanied by intestine, being herniated through

the rent in the diaphragm, (3) the presence of very bloody fluid in the left chest. The features which should have suggested the proper diagnosis were: the history of a penetrating wound in the lower left thorax, the marked vomiting not productive of bile-stained fluid, the dislocation of the heart to the right, and the dullness in the left lower thorax.

Diaphragmatic herniae have been classified by Astley Cooper<sup>1</sup> into three categories: (1) Congenital: due to defects in the diaphragm arising from faulty embryologic development, (2) acquired: which develop at points of anatomic weakness, e.g. at the esophageal hiatus, aortic, or caval openings, and (3) traumatic; caused by rents in the diaphragm arising from direct or indirect trauma.

Strangulation is infrequent in both congenital and acquired diaphragmatic herniae. Cooper<sup>1</sup> in 1798 described a case of the former, noting: "When the congenital opening of the diaphragm is small, consequences are not immediately fatal. It produces some inconveniences which increase in the progress of life and at length destroys as in other herniae by a strangulation of protruded parts." Usually, however, the congenital defect is large and consequently admits ingress and egress of large portions of coelemic organs without serious constriction. In our series of 43 cases with strangulation only four were congenital, and 34 were traumatic.

Traumatic diaphragmatic hernia constitute over 90 per cent of cases complicated by strangulation, and for this reason we have particularly directed our attention toward this type. From an etiologic viewpoint this type of hernia falls into three main classifications, (1) those caused by stab wounds of the thorax, (2) those caused by gunshot wounds of the thorax, and (3) those caused by indirect violence to the diaphragm, such as falls, compression injuries, and steering wheel accidents.

Traumatic diaphragmatic hernia showed an increased incidence during and immediately after the first world war, and will undoubtedly show a similar tendency following the recent conflict. Wounds of the diaphragm are not prone to heal, and many observers believe that upon severance of the diaphragm negative pressure in the thorax causes ascent of intra-abdominal organs through the new orifice. A portion of omentum plugs the opening and at the same time separates the muscle fibers, preventing their subsequent union. The opening is thus maintained as a constant mortal threat to the patient. Thirty-four of the cases in the present study were traumatic in origin, the initial factor being stab wounds in 38.2 per cent, gunshot wounds in 38.2 per cent, and indirect trauma in 23.5 per cent. Five cases of the total group were of undetermined etiology, and four were congenital.

#### SYMPTOMS

Premonitory symptoms referable to the abdomen or thorax were noted prior to the acute attack in 30.2 per cent of the total group. All but one patient with premonitory symptoms gave a history of previous trauma. Typical symp-

toms included sporadic pain, usually located in the left thorax or left upper quadrant of the abdomen; less commonly, flatulence, constipation, and vomiting were noted; and still less frequently, dyspnea and cyanosis occurred.

The interval between the initial injury and the acute attack can be extremely variable, as short as one day or as long as 16 years. In 85 per cent of the cases, however, strangulation occurred within three years after injury.

The acute attack usually begins abruptly; in 29 instances the attack was definitely stated to have been sudden in onset. In 85 per cent of the traumatic cases, relatively sudden increase in the intra-abdominal pressure was noted as a precipitant of the acute attack. Eating or drinking was cited in 9 cases, physical stress in 8, and straining at stool in one.

Pain, vomiting, constipation, dyspnea, and hiccoughing are symptoms commonly noted during the acute attack. Pain, characteristically sudden, has been the most usual initiating symptom. Specifically mentioned in 37 instances, pain was noted in various locations, and often in a combination of anatomic areas. In 44 per cent of the cases there was pain in the left upper quadrant; in 30 per cent in the left thorax; in 16 per cent in the epigastrium; in 7 per cent in the right lower quadrant; in 10 per cent around the umbilicus; and in 27 per cent there was generalized abdominal pain. Most characteristically the pain has been located in the upper portion of the abdomen, and has frequently been associated with pain in the inferior portion of the left thorax. It is commonly severe and colicky, and may prostrate the patient. Although many writers have stressed radiation of pain into the left shoulder, it was found in only 11 per cent of the 43 reported cases.

Vomiting was specifically mentioned as occurring in 88 per cent of the cases, usually simultaneous with, or soon after, the onset of pain. In some instances it was the initial complaint. In cases in which the stomach has been strangulated, vomiting is early, protracted, and ineffectual, frequently with evidence of blood.

Although the incidence of hiccough has been relatively infrequent, having been found in 4 cases, or 10 per cent of the total, its presence is important as being suggestive of diaphragmatic irritation.

Constipation was mentioned specifically in 21 instances in this series, or a total of 49 per cent of the cases. It frequently preceded the onset of the acute attack and probably represents a precipitating factor since it likely caused increased abdominal pressure and thus sponsored the tendency for strangulation. When it manifests itself during the acute attack it is associated with other signs of acute intestinal obstruction such as abdominal distention, hyperactive peristalsis, and the inability to pass flatus or feces. It is well to emphasize that these symptoms during the acute episode are similar to those associated with obstructions of the colon. Although constipation has been associated with strangulation of the stomach, in such instances it generally precedes the attack and is not complete. Thus the effectual movement of the bowels, the presence of an undistended abdomen, and normal peristaltic intes-

tinal activity have presented serious confusion to the observer in those instances in which the stomach alone is strangulated. The obvious signs of acute obstruction are most prominent when the obstruction is located in the intestinal tract; they are not nearly so emphatic in cases of obstruction at the stomach.

Dyspnea was mentioned in 15 or 35 per cent of the cases. Appearance of this symptom depends largely on the suddenness and the degree of encroachment by the herniated portions and the accumulated fluid upon the cardio-respiratory system.

#### PHYSICAL FINDINGS

The diagnosis of diaphragmatic hernia was always a matter of extreme difficulty prior to the advent of roentgenology. Bowditch<sup>4</sup> in 1853 collected 88 cases of diaphragmatic hernia available in the literature to that time and presented one case of his own. His own and one other were the only cases diagnosed before autopsy up to that time. With roentgenology a formidable method of establishing diagnosis has been acquired. It should be emphasized, however, that in strangulated diaphragmatic hernia at least one or more abnormal physical signs are present in the thorax which should direct attention to this part of the body. Gibson<sup>13</sup> in 1930 reported three cases of strangulated diaphragmatic hernia which he diagnosed clinically without aid of roentgenology. He stressed the importance of the clinical signs in such cases, and the necessity of appreciating them, in view of the fact that many of these patients were so acutely ill as to prevent necessary roentgenologic examination. In one of our cases the correct diagnosis was considered, but roentgenologic confirmation could not be obtained because of the patient's precarious condition. Gibson stressed the following diagnostic symptoms: (1) Diminished expansion of the chest, (2) impairment of resonance, (3) adventitious sounds, (4) cardiac displacement, (5) circulatory collapse, (6) cyanosis and dyspnea, and (7) asymmetry of hypochondria.

Physical findings in the abdomen are in no way diagnostic. Attention is generally focused on the abdomen because of the presence of pain in some region, which as such is usually misleading. As pointed out, the pain is usually located in the upper portions of the abdomen and there is associated tenderness to palpation in those areas. As with other types of intestinal obstruction, when the obstruction is low the pain is very apt to be generalized, the abdomen may be distended, and other evidences of intestinal obstruction may be present. If the stomach is obstructed, the abdomen may be scaphoid and in other respects quite normal in appearance. Some observers have placed importance on unusual concavity of the left hypochondrium representing the area voided by migration of abdominal viscera into the thorax. This finding is apparently quite rare, and did not occur in any of our cases.

The greatest emphasis must be placed upon physical examination of the chest. Records given in the literature of examination of the chest have been somewhat incomplete. Physical examination was recorded in 30 of the 43 cases analyzed. In 27, or 90 per cent of these, at least one of the following was



present: (1) Dullness in the left thorax, found in 18, or 60 per cent of the cases; (2) cardiac shift, found in 14 cases, or 47 per cent; (3) tympany of the left thorax, occurring in 13 cases, or 40 per cent; adventitious sounds (gurgling, tinkling, or peristaltic sounds in the thorax), found in six cases, or 20 per cent; and (5) succussion splash, found in two cases, or 6 per cent.

Fluid has been found in the thorax either on physical examination, at operation, or at autopsy in 12 of the 43 cases (30 per cent). The character of the fluid was described in nine of these, *and in eight was noted to be bloody or sero-sanguinous*. This is a point of special interest, since in one of our cases and in two other cases—one reported by Deaner, McMenemey, and Smith<sup>29</sup> in 1943, and another by Pfahl and Lund<sup>32</sup> in 1944—the diagnosis was confused by the bloody fluid in the thorax and the failure to recognize that as much as 3½ liters may be found in conjunction with strangulated diaphragmatic hernia. This fluid may closely resemble blood and in one case a RBC count of 1.9 millions per cc. was noted. Deaner, McMenemey, and Smith were the first to point out the possible occurrence of sero-sanguinous effusion with strangulation, but its presence in the thorax has been noted at necropsy in reports as far back as Astley Cooper. This clinical finding deserves special significance. It unquestionably occurs more often than has been reported and should occur in all cases of strangulated diaphragmatic hernia except those of short duration, since the pathologic physiology differs in no way from strangulation in other types of herniae where bloody fluid is commonly seen.

Roentgenograms were made in 21 cases, with correct diagnosis in 16. As far as roentgenologic examination is concerned, the points which were found to be important are: (1) The simulation by the herniated viscus of high diaphragm. In a case with radiologic evidence of an apparently high diaphragm and an accompanying history of previous thoracic injury, the patient should be considered a candidate for diaphragmatic hernia until proven otherwise. (2) Cardiac shift to the right is almost always present and is noteworthy. Physicians may be apt to rationalize cardiac shift on the basis of high diaphragm or by the presence of what appears to be fluid in the left thorax. Cardiac shift does not normally accompany elevated diaphragm and is not apt to be present unless there are large amounts of fluid or viscera in the thorax. (3) In many instances the presence of air bubble above the normally anticipated level of the diaphragm establishes diagnosis immediately. This gas bubble need not appear, however, and the presence of a homogenous density below a somewhat convex border presumed to be diaphragm may be misleading. In one instance (Case 1) the stomach was herniated above the diaphragm, the superior border of the stomach simulated the arch of the diaphragm, and there was no air in the stomach. The diagnosis of diaphragmatic hernia was thought to be impossible. (4) Patients often show roentgenologic evidence of fluid in the thorax.

The transverse colon is the portion of the gastro-intestinal tract which most frequently herniates into the thorax. Tabulation reveals that the herniated organs were as follows: transverse colon, 23 times, or 53.4 per cent;

stomach, 20 times, or 45 per cent; small intestine, 11 times, or 25 per cent; splenic flexure, 10 times, or 23 per cent; descending colon, five times, or 11.5 per cent; colon (site undesignated), four times; spleen, twice; and ascending colon, once. The most frequent occurrences were: stomach alone, eight times; transverse colon alone, seven times; splenic flexure alone, seven times; stomach and transverse colon, four times; stomach and small intestine, four times; and splenic flexure and transverse colon, three times.

It becomes quite clear from a perusal and statistical analysis of the case histories that in traumatic diaphragmatic hernia, which comprise the greatest percentage of those cases which become strangulated, a singularly common pattern of events ensues and presents a rather typical picture. The patient is commonly a male previously in good health. Review of his past history will reveal a traumatic episode involving the thorax either by a stab or gunshot wound in the region of the diaphragm or by a severe contusion. He is seized suddenly with acute pain generally located in the upper abdomen, most frequently in the left upper quadrant, and associated with pain in the lower portion of the left thorax. A cardinal symptom, radiation of pain to the left shoulder, is sometimes present, and directs attention to the diaphragm immediately. Characteristically the pain is precipitated while eating, drinking, or exercising. Almost simultaneously with the onset of the pain, the patient begins to vomit and continues to do so without relief. Thereafter he develops signs of acute high or low bowel obstruction, depending on the viscus involved. Physical examination will reveal one or more signs directed to the left thorax. Usually dullness or tympany of the left thorax is present inferiorly with concomitant suppression of breath sounds. In a great number of cases there is cardiac shift to the right. Occasionally extraneous bowel sounds in the chest, in themselves pathognomonic of hernia, are detected. Aspiration of the left thorax based upon physical signs will reveal bloody fluid. Roentgenologic examination will frequently reveal cardiac shift to the right and one of the following findings: (1) a recognizable portion of the gastro-intestinal tract in the left thorax above the diaphragm, most frequently a loop of large intestine, (2) an apparently very high left diaphragm, (3) fluid in the left thorax.

To recapitulate, the following should suggest the diagnosis of strangulated diaphragmatic hernia: (1) signs of acute gastro-intestinal obstruction, (2) history of an old injury, (3) physical findings referable to the left thorax, particularly cardiac shift to the right and, on occasions, bloody fluid on aspiration, and (4) roentgenologic evidence of a high left diaphragm.

#### TREATMENT

It may seem trite to emphasize that the treatment of strangulated diaphragmatic hernia is emergency surgery. Hedblom<sup>36</sup> pointed out in 1925 that when obstruction develops the mortality is doubled. In 126 collected cases with acute intestinal obstruction he found the mortality to be 53.1 per cent.

In our collected series of 39 cases of strangulated diaphragmatic hernia, the mortality for the period 1798 to 1919 was 88.8 per cent, with an operative

mortality rate of 66 per cent. For the period 1920 to 1945 the general mortality rate was 57.1 per cent and the operative mortality 43.7 per cent. In our own series of four cases, the mortality rate was 25 per cent.

The senior author emphasized in 1935 the advisability of utilizing the transthoracic route for the attack on diaphragmatic hernia.<sup>34</sup> Such an approach is especially suited for small hernia since it allows the operator to investigate the diaphragm under excellent visual conditions. When there is no strangulation of the viscera the incision is adequate for the reduction of the organs and successful repair of the hernia. When a large amount of viscera has been strangulated the thoracic incision should be extended across the costal margin into the abdomen. Opportunity to inspect the strangulated abdominal organs is afforded, and the operator can understand the pathology of viscera below the diaphragm as well as utilize the previously mentioned advantages of better exposure and easier reduction of the hernia afforded by the thoracic approach. We believe that the combined thoraco-abdominal approach should be considered in all cases of strangulated diaphragmatic hernia but that the initial incision should be made thoracically rather than abdominally, and the extension across the costal margin into the abdomen made when the exact circumstances have been appraised from above. The reasons for the thoracico-abdominal approach have been emphasized by Carter,<sup>35</sup> who cites the conclusive advantages: (1) excellent exposure is provided, (2) the herniated viscera are often adherent to the lung, the thoracic wall, or the diaphragmatic ring, and must be freed from above under direct vision, (3) access to the diaphragmatic orifice is easily gained, (4) when tears are located near the heart, sutures can be placed accurately and with less danger of wounding the heart, the esophagus, and the mediastinal vessels than might occur with an abdominal incision alone.

#### CASE REPORTS

**Case 2.** (Previously reported by B. N. Carter<sup>34</sup>).—G.H., colored female age 45, was admitted to the Cincinnati General Hospital on October 1, 1933, complaining of cramp-like pains in the abdomen. Ten weeks before admission she had fallen from a third story window and suffered a central dislocation of her left hip. She was a patient in the Cincinnati General Hospital at that time for seven weeks. During her first hospital stay there were no symptoms referable to the abdomen or to the thorax but physical examination on discharge from the hospital revealed some dullness at the left base of the chest. Two days before the second hospital admission the patient began to have cramp-like pains in the abdomen immediately after eating a large plate of pork and beans. These pains occurred particularly in the upper right quadrant and in the lower left thorax. *The pain was referred sharply to the shoulder and somewhat into the left neck.* There was a sensation of suffocation and palpitation. The patient had vomited almost everything she had eaten the previous day and there had been obstinate constipation for two days.

Physical examination showed a thin, gray haired negress who was suffering acute cramp-like pains and was screaming with agony. Examination of the thorax disclosed dullness and flatness in the lower left portion. Auscultation showed striking peristaltic noises in the thorax which could be heard without the aid of a stethoscope. The abdomen was slightly rounded and tense. No peristaltic patterns could be seen although a great many peristaltic sounds were heard over the abdomen. A diagnosis of dia-

phragmatic hernia with intestinal obstruction was made. This was confirmed by roentgenologic examination with the patient in a sitting position. The outline of the large bowel could be seen in the lower left thorax without the aid of opaque material.

The patient was operated upon immediately. A high mid-line incision was made in the epigastrium, and dilated large bowel was seen which disappeared through a defect in the diaphragm. Some of the large bowel was reduced through the opening into the abdomen but complete reduction could not be effected until the opening in the diaphragm had been enlarged by a lateral incision. Nine inches of colon were found in the thorax. The bowel was dark red in color and there were about 150 cc. of blood-tinged fluid in the left pleural cavity. The opening in the diaphragm was immediately anterior to the esophagus. The edges of the ring were indurated and fibrotic, indicating that the hernia had been present for some time. There was no sac present. The rent in the diaphragm was closed with double medium silk sutures and the abdomen was closed in the usual way. Convalescence was uneventful. Subsequent roentgenograms have shown the hernia to be cured.

#### COMMENT

The diagnosis in this case was suggested by the pain referred to the left shoulder and was confirmed by the presence of pathognomonic peristaltic sounds in the left thorax and by roentgenologic examination which, without the aid of barium, revealed a dilated loop of bowel above the diaphragm. The circulation in the involved bowel was impaired, as evidenced by the dusky red color and a small amount of bloody pleural fluid. In this instance the diaphragm had been ruptured by indirect violence.

Case 3.—E.L., white male age 26, was admitted to the surgical service on December 26, 1944. One week earlier he had been seen in the receiving ward of the Cincinnati General Hospital complaining of sharp sudden lower abdominal pain of knife-like character, associated with nausea and vomiting. A diagnosis of gastroenteritis was made and he was referred to his local physician. For the ensuing seven days he was bedfast at home, suffering with severe abdominal pain which became more generalized and then moved to the left flank and the left costovertebral angle. During that time he vomited frequently, had no bowel movements, and did not pass any flatus. Past history revealed that he had been admitted to the Cincinnati General Hospital for a penetrating gunshot wound of the thorax on March 15, 1943, at which time it was thought likely that the bullet had traversed both lungs and had probably perforated the lower end of the esophagus. While in the hospital he developed a bilateral hemothorax, pericarditis without effusion, and on his 14th hospital day had a sudden internal hemorrhage manifested by several tarry stools. He recovered with conservative therapy and was discharged on April 13, 1943.

Physical examination revealed an acutely ill male, temperature 100.4, blood pressure 96/70. A healed gunshot wound in the mid-axillary line at the level of the 6th rib, and another on the posterior aspect of the right thorax were found. Percussion note was hyporesonant over the left base posteriorly. Breathing was grunting in character. The heart was not enlarged to percussion and sounds were distant and weak, with rhythm being regular. The abdomen was moderately distended with slight voluntary spasm chiefly on the left side, and was absolutely quiet. No masses or organs were felt. Laboratory tests revealed the following: WBC, 12,400; hemoglobin, 13.5 Gms.; urine, negative; serum chlorides, 340. A flat film of the abdomen showed many dilated loops of small bowel with multiple fluid levels. Diagnosis of intra-abdominal abscess with resultant ileus and obstruction was made.

On December 27, 1944 he was noted to have signs of fluid in the left thorax. Thoracentesis was performed and 150 cc. of foul smelling *serosanguinous* fluid were with-

drawn. This fluid had a specific gravity of 1.020, and on smear was found to contain gram positive cocci and gram negative rods. Diagnosis of strangulated diaphragmatic hernia with empyema formation was made. Roentgenologic examination of the thorax revealed marked displacement of the heart to the right and congestion in the left lung field. Barium enema showed the colon to be normal as far as the splenic flexure, where there was an annular constriction 2-3 cm. in length through which a very small amount of barium passed.

Because of the patient's poor condition, cecostomy and closed thoracostomy were immediately performed, followed on January 3, 1945 by a Devine colostomy, and repair of the hernia by the thoracic route on February 27, 1945. On May 1, 1945 the colostomy was resected with end-to-end anastomosis. Postoperative course throughout these procedures was stormy, and the patient signed out against advice on May 14, 1945.

#### COMMENT

This case presents several interesting features. It exemplifies one possible development if a strangulated hernia is allowed to progress unrecognized and if the perforation of the bowel occurs into the thoracic cavity. In such cases empyema develops and it is probable that certain of these cases have been treated for their pleural disease without recognition of the underlying pathology. Such a case was reported by Slater and McKenzie<sup>20</sup> in 1923. Their patient was operated upon for intestinal obstruction of undetermined cause located at the splenic flexure. Because of the patient's poor condition, a cecostomy was performed, following which he did well but developed purulent fluid in the left chest. A rib resection was done, the pleural cavity drained, and the patient recovered. He was re-admitted to the hospital eight months later with severe abdominal crampy pain, vomiting, hiccough, and dullness of the left lower lobe. He subsequently died, and autopsy revealed herniation of the transverse colon and the cardiac end of the stomach through a rent in the diaphragm.

Our case illustrates a similar method of treatment in such instances; that is, a cecostomy for decompressing the bowel plus local drainage at the site of strangulation. The repair of the hernia can then be undertaken from the thoracic route at some future date when the patient is in suitable condition.

The correct diagnosis was not immediately arrived at in this instance though there were present a history of penetrating wound of the chest in the region of the left diaphragm, signs of intestinal obstruction, physical findings referable to the lower left thorax, and displacement of the heart to the right. Only after bloody foul smelling fluid had been aspirated from the thorax was the proper diagnosis suspected and confirmed by barium enema.

**Case 4.**—W. H., colored male, age 35, was seen in the receiving ward of the Cincinnati General Hospital on May 31, 1947 by a medical consultant. His illness began suddenly 6 days previously when, following an alcoholic debauch, he was seized with acute agonizing pain in the epigastrium with radiation into the left thorax and into both shoulders. He immediately vomited and continued to do so on the days following. He was severely constipated and passed no feces or flatus except for two or three lumps of hard stool after an enema. Past history revealed he had suffered a skull fracture in 1920 and a stab wound of the left lower chest in 1939.

## STRANGULATED DIAPHRAGMATIC HERNIA

Physical examination revealed a sweating, orthopneic, dyspneic colored male. Temperature was 100.2; blood pressure, 130/90; pulse, 120; respirations, 40. Dullness to flatness was noted on percussion over the left lower thorax and absent to diminished breath sounds were noted in the same area. A stab wound scar was present over the 7th rib in the left anterior axillary line. The abdomen was diffusely distended. There was voluntary muscle spasm but no localizing tenderness. No peristalsis could be heard.

Clinical diagnosis was left lower lobe pneumonia with paralytic ileus on the basis of the pneumonia. A chest film was secured and revealed what was thought to be a high left diaphragm. The diagnosis of a probable subphrenic abscess was now entertained and surgical consultation was requested. The tentative diagnosis of strangulated diaphragmatic hernia was made on the basis of the medical consultant's report, and upon examination of the patient these confirmatory findings were elicited: The left thorax was noted to be dull posteriorly as previously described and, in addition, the lower portion anteriorly was decidedly tympanitic; the apex beat of the heart was noted to be in the fourth interspace to the right of the sternum; review of the chest film revealed that the heart and mediastinal structures were shifted to the right, a homogeneous density containing an area of radiolucency was seen to occupy the lower half of the lung field, and the left diaphragm could not be identified; flat and erect films of the abdomen showed the pattern of large bowel obstruction, and gas was noted to be present in the large bowel as far distally as the splenic flexure; upon barium enema the bowel could be filled only up to the splenic flexure.

Operation was performed immediately by a combined thoraco-abdominal incision. A portion of the transverse colon and the splenic flexure had herniated into the thorax through an opening in the anterior half of the left diaphragm that would accommodate only two fingers. Approximately 600 cc. of non-odorous bloody fluid were found in the pleural cavity. The 10-inch segment of herniated colon was severely dilated and purple in appearance. Upon reduction its color improved noticeably but there was a 4 cm. area of bowel which retained a mottled black appearance and was of questionable viability. The strangulated bowel was reduced into the abdomen after the opening in the diaphragm had been greatly enlarged. The thoracic portion of the wound was closed after the diaphragm had been repaired. The questionable loop of bowel was exteriorized as a double barreled colostomy and the abdominal wound closed with silver wire. In addition, a cecostomy was performed. His postoperative course was very satisfactory. On the third postoperative day his wound was dressed and it was discovered that the segment of bowel in question had actually been non-viable and was now completely gangrenous. This portion of the bowel was resected without anaesthesia being required. He was maintained on penicillin and sulfadiazine therapy. Clinical signs of fluid developed in the left thorax on the 15th postoperative day and a thoracentesis was performed on the 17th day with the removal of 1000 cc. of straw-colored fluid which was negative on culture. His course thereafter was afebrile, and on July 7, 1947 the colostomy was closed by side-to-side anastomosis. He was re-admitted on October 27, 1947 and the cecostomy was closed on October 30.

This case illustrates the ease with which diagnosis can be made in these cases when one is cognizant of the signs and symptoms of strangulated diaphragmatic hernia. Case 1 had been so striking and so recent that the similarity with this case could be noted even in the history. The diagnosis was readily made in view of the history of previous penetrating wound of the left lower thorax, the signs of intestinal obstruction, the displacement of the heart, the roentgenologic findings suggesting a high diaphragm on the left, and the signs of fluid in the left chest. No thoracentesis was performed, but at operation there were 600 cc. of very bloody fluid in the thorax. A combined incision

was made on account of the hugely distended loop of colon which occupied a large part of the left pleural cavity and which could not be reduced through the exposure afforded by either a thoracic or an abdominal approach.

## SUMMARY

In a review of 39 cases from the literature together with four cases from our own hospital records, the clinical picture of strangulated diaphragmatic hernia is presented. Emphasis is placed on the striking consistency of the history and physical findings as follows: (1) history of a previous thoracic injury, (2) physical findings referable to the left chest, particularly displacement of the heart to the right, dullness or tympany in the lower portion of the thorax, adventitious sounds, and aspiration of bloody fluid from the left pleural cavity, (3) roentgenologic findings suggestive of a high left diaphragm with displacement of the heart to the right, and (4) signs of acute gastrointestinal obstruction with particular emphasis on the fact that where the stomach alone is strangulated there is absence of abdominal distention and a patent intestinal tract.

The use of a combined thoraco-abdominal incision is recommended in the surgical treatment.

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## RECONSTRUCTION OF THE EXTERNAL EAR\*†

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RECONSTRUCTION OF THE EXTERNAL EAR to correct for substance lost by reason of congenital, post-infectious, or posttraumatic defects, or following excision of malignant tumor, represents one of the most difficult problems in plastic surgery. An abnormal ear is conspicuous and an absent one is a major cephalic deformity. Criteria for successful reconstruction have been set down by Suraci who lists seven points as essentials if the reconstruction is to be acceptable to patient and to surgeon. These are: correct size, similarity of outline, similarity of height, correct cephalo-auricular angle, permanency of size and shape, rigidity of the ear and matching color. The earliest attempts at reconstruction of the ear fell far short of this goal.

Survey of the literature reveals that Tagliacozzi,<sup>2</sup> in the 16th century, referred to the repair of partial losses of the ear by the use of flaps of skin from the scalp or neck. Also, Dieffenbach,<sup>3</sup> in 1830, outlined the reconstruction of partial defects by the use of local flaps. In 1870, Szymanowski<sup>4</sup> reported his technic for subtotal reconstruction of the external ear. The method utilized the principle of the local flap, outlined in butterfly shape on the scalp, then elevated and folded on itself. In 1907, Nelaton and Ombredanne<sup>5</sup> proposed a local flap for partial loss of the ear, providing rigidity by the insertion of a free graft of cartilage. Gillies<sup>6</sup> (1920) embedded free grafts of cartilage in the auricular area, elevating the constructed pinna into position at a second operation. Van Dijk<sup>7</sup> (1926) reported one case of total loss of the ear following a burn by electricity. He used a compound cervico-thoracic flap incorporating costal cartilage. De River<sup>8</sup> (1927) utilized the Szymanowski "butterfly" flap combined with a tubed pedicle. Graham<sup>9</sup> (1927) used septal cartilage as a buried transplant, reflecting a flap of skin from behind the ear at the second stage of the procedure. Graham also reported a case of Pierce<sup>10</sup> in which buried costal cartilage had been elevated and backed with a stent graft of skin after which a thoracic tubed pedicle was transplanted to simulate the helix of the ear. Pierce<sup>10</sup> (1930) reported four cases in which he used free cartilage as an inlay graft combined with a cervical tubed pedicle to construct the helix. Lockwood<sup>11</sup> (1930) reported two cases constructed by the use of pedicled flaps of soft tissue. The results were not comparable to those of Pierce. New<sup>12</sup> (1931) published photographs of one case of partial traumatic loss repaired by a tubed flap from the thoracic area. Easer<sup>13</sup> (1935) used foreign material, hard rubber, to supply rigidity to the reconstructed ear. Padgett<sup>14</sup> (1938) reported four cases in which he had used Pierce's technic modified

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## RECONSTRUCTION OF EXTERNAL EAR

by the use of a split flap of soft tissue. Newman<sup>15</sup> (1941) reported two cases in which Pierce's technic had been used with gratifying results. Gillies<sup>16</sup> (1937) reported on his failure in one case to make use successfully of a pedicled flap supported by carved grafts of iliac bone. He also listed cases in which

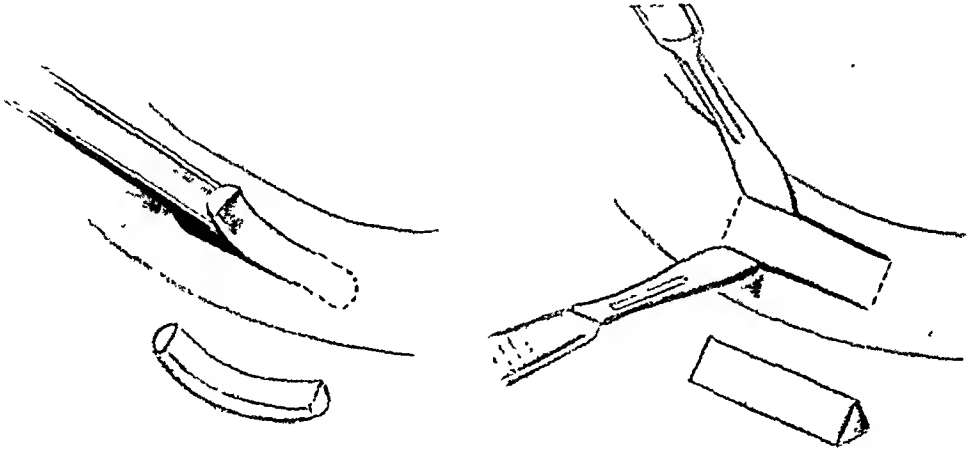


FIG. 1.—The technic of cutting free cartilage grafts by gouge as shown at the left causes compression of the cartilage so that some degree of distortion or curling of the graft is unavoidable. The use of two scalpels as shown at the right prevents abnormal compression of the cells and minimizes the tendency to curling.

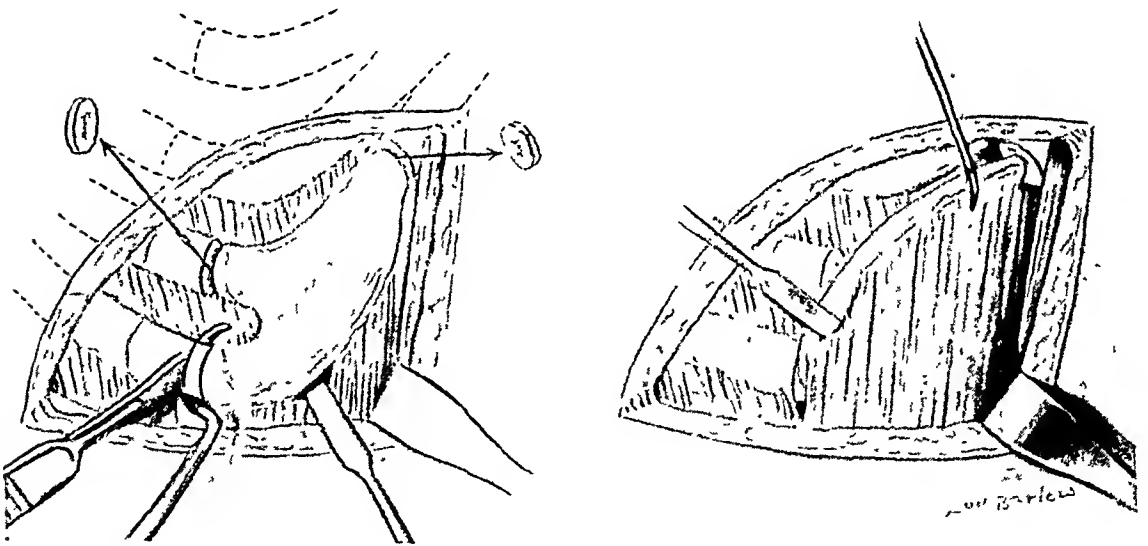


FIG 2.—Sketch showing the technic of cutting the costo-chondral cartilages so that a large free graft may be obtained from the site of fusion of two cartilages. The excision of a disc, 2 to 3 mm. in thickness, at the level of each transection facilitates the removal of a large block of cartilage.

cartilage from the maternal ear was substituted as a homoplastic graft for the absent auricle. This type of transplant was successful in five of seven cases. Nattinger<sup>17</sup> (1937) also reported two cases in which maternal ear cartilage had been used successfully. Pierce and O'Connor<sup>18</sup> (1938) used preserved cartilage from cadavers or living cartilage from the ear of the mother. Kirk-

ham<sup>19</sup> (1940) also reported on the use of cadaver cartilage for reconstruction of the ear. In his technic the dead cartilage was perforated freely and soaked in solution of formalin to establish rigidity of the graft. A further report by Gillies<sup>20</sup> (1941) listed 16 cases in which cartilage from the mother's ear had

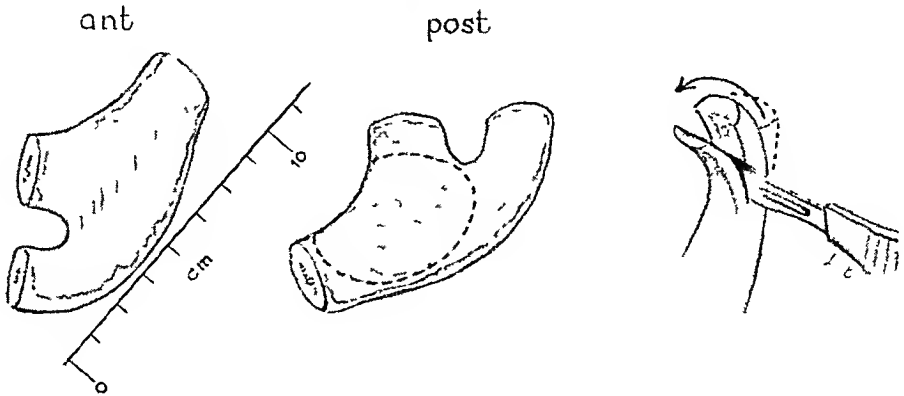


FIG. 3.—Sketch showing the anterior and posterior aspects of a specimen of costochondral plate at the level of fusion of the cartilages of the 8th and 9th ribs. The posterior aspect of such a specimen is concave. As the costal cartilage is thinned by carving, advantage is taken of the tendency of such cartilage to curl, in order to exaggerate this concavity. The transplant is embedded under the skin of the auricular region in such a way that the concavity of the graft assumes the position of the concha of the normal ear



FIG. 4.—Case 1 (a) congenital microtia corrected by use of a cervical tubed pedicle (b) pedicle detached at its lower end and sutured to upper portion of pinna (c) appearance after suture of the tubed pedicle to the ear.

been transplanted to the child; 11 of these were considered successes. In two cases there was aseptic absorption of the cartilage and in three the grafts were lost due to sepsis. Greeley<sup>21</sup> (1941) used this method but later reported that there was absorption of the maternal cartilage. Young<sup>22</sup> (1940), in animal experimentation, observed that strips of costal cartilage healed by cartilaginous union when transplanted to articular surfaces. Then, in 1941, Young<sup>23</sup> pre-

sented a new idea. In animal experiments he determined that autogenous costal cartilage, finely chopped and seeded over the fascia of the rectus muscle, stayed viable and fused into a solid sheet of opaque "cartilage-like" tissue. The fused areas were found to consist of fibrous tissue. Grossly this tissue had some of the properties of fibro-elastic cartilage. Peer<sup>24</sup> (1943) reported on the



FIG. 5.—Case 2 (a) Congenital microtia. (b) Appearance after implantation of carved costal cartilage. (c) After elevation of cartilage graft and backing with a split graft of skin. Further revision of the tissue of the helix is necessary in this case.

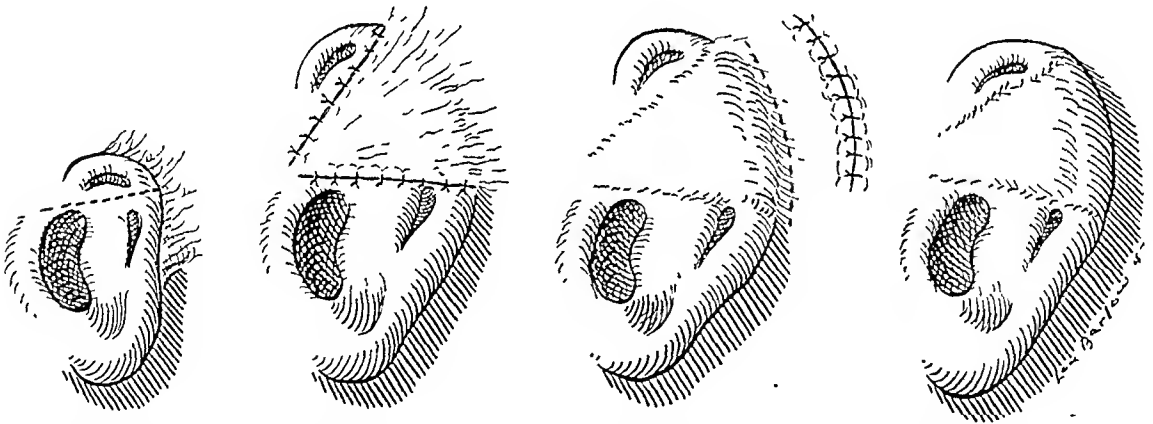


FIG. 5.—(d) Sketch of operative steps involving the transverse section of the rudimentary ear, rotation of the superior and inferior portions and their suture to the skin of the post-auricular area, the implantation of a carved graft of costal cartilage and the elevation of the graft from the head and its backing with split skin graft.

use of finely chopped pieces of cartilage as grafts in the reconstruction of the external ear in humans. He referred to such finely chopped costal cartilages as "diced cartilage grafts." In 1943 he<sup>25</sup> reported on the accurate formation of such fibro- cartilage into the shape of auricular cartilage by the use of a perforated bi-valved mold of vitallium which had been filled with "diced" cartilage and buried in the abdominal wall for three months. This fibro-cartilaginous

framework was then successfully transplanted beneath the skin of the aural area. Young<sup>20</sup> (1944), using a perforated mold of ticonium, cast fibro-cartilaginous grafts in the shape of the auricular cartilage. He reported one case

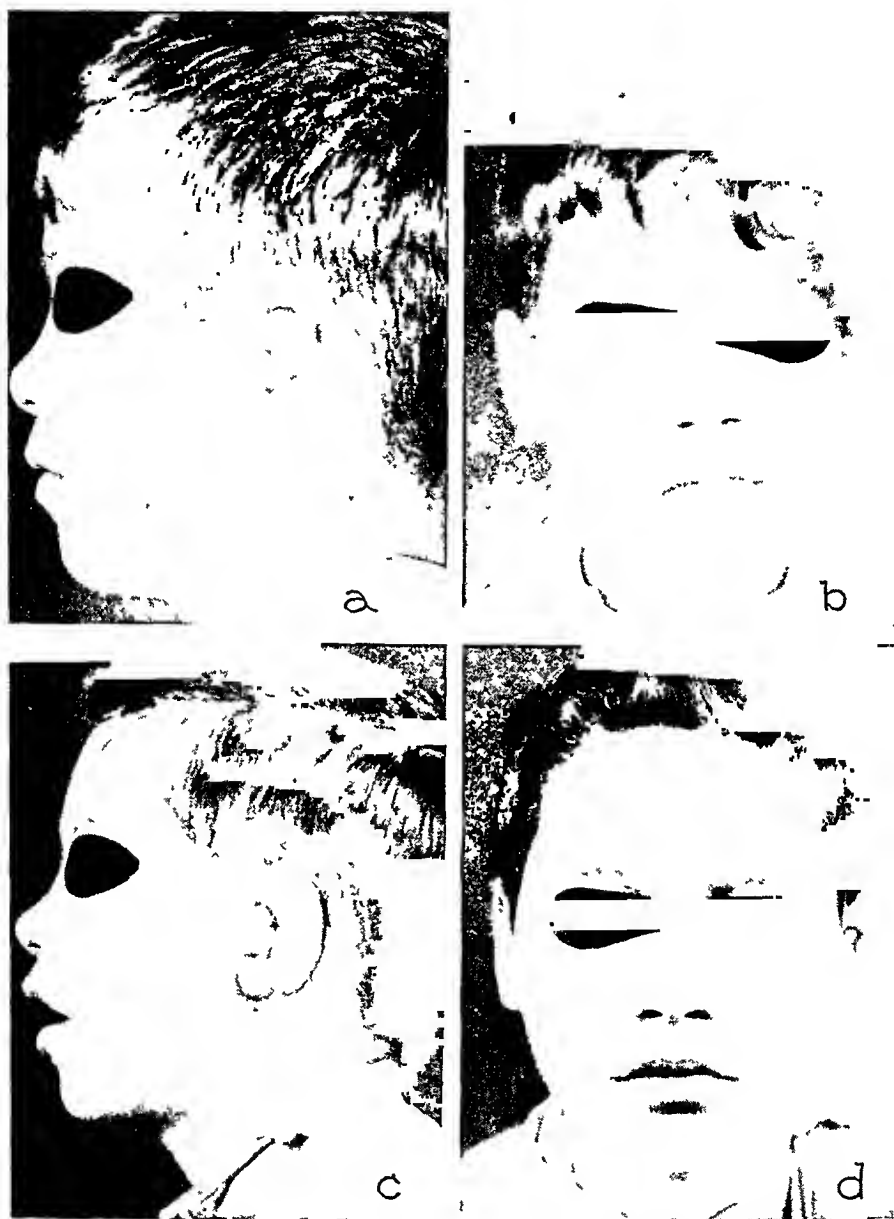


FIG 6.—Case 3 (a and b), Congenital absence of the ear. (c and d), Appearance after reconstruction by use of a carved graft of cartilage and its elevation and backing with a split skin graft

in which the principle was applied to the construction of the external ear. Aufricht<sup>27</sup> (1947) reported on the pre-casting of auricular cartilage by the use of a perforated acrylic mold, filled with flat chips and thin platelets of cartilage and buried in the abdominal wall. He emphasized the necessity for the use of a generous flap from the scalp in the creation of the concha, recognizing that

the pressure of a tight cutaneous flap tends to obliterate the contours of auricular cartilage which have been constructed by this method. This experience of Brown et al<sup>28</sup> (1947) in reconstruction of the ear indicated that suitable reconstruction of the external ear can be accomplished by the use of carved costal cartilages. They emphasized that reconstructive surgery of this magnitude need not be prolonged but can be accomplished in cases of loss of helix or pinna in only two stages and that total reconstruction of the ear can be completed in three operative stages.



FIG. 7.—Case 4 (a). Congenital absence of the ear. (b) Appearance after implantation of large, carved graft of costal cartilage. (c) Appearance after elevation of cartilage and application of split graft of skin behind the ear. Reconstruction in two stages.

During the past two years the authors have had experience with ten cases of reconstruction of the external ear. These were managed on the Surgical Service of The New York Hospital and on the Plastic Surgery Service of the U. S. Veterans' Hospital,\* Bronx, New York. The general principles of the technic of Pierce have been followed with agreement in execution with the advancements of Brown et al. In several cases subtotal reconstruction of the ear has been carried out in two stages. The authors have had no experience with molded cartilage grafts. The management of cases included in this report has led to the opinion that suitable reconstruction of the external ear can be accomplished if sufficient attention is given to the cutting and the carving of costal cartilage, to the importance of the establishment of a lateral concavity to represent a concha, and to the many minor details which enter into the execution of this type of reconstructive surgery.

#### CARVING OF COSTAL CARTILAGE

Experience in the handling of fresh costal cartilage has led to observations which have contributed to success in obtaining a suitable restoration of the

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external ear. A common objection to the use of straight grafts of cartilage in reconstructive surgery is that, after transplantation, the graft may undergo distortion of shape, curling. Figure 1 shows the technic of cutting grafts from



FIG. 8.—Case 5 (a and b) Congenital absence of the ear in association with facial asymmetry. (c and d) Appearance after reconstruction by implantation of carved costal cartilage, elevation of the cartilage and backing with a split skin graft and use of a tubed pedicle to simulate the appearance of the helix.

costal cartilage by gouge and by scalpel. The use of a gouge causes compression of medullary and cortical cells of the costal cartilage in such a way that, even after carving, the graft tends to warp or curl. The use of two scalpels as shown prevents abnormal compression of cells and minimizes this tendency. On microscopic examination of the transversely cut edge of costal cartilage it

is apparent that the center of the cartilage is yellow and the periphery is grey. The gross structure of the costal cartilage is somewhat similar to that of bone. It is stated in Gray's<sup>29</sup> "Anatomy" that "in the thickest parts of the costal cartilages a few large vascular channels may be detected. This appears, at first sight only, to be an exception to the statement that cartilage is a non-vascular tissue; actually the vessels give no branches to the cartilage substance itself, and the channels may rather be looked upon as involutions of the perichondrium." This gross structure apparently causes a variation in tissue tension when the costochondral cartilage is cut or carved. Figure 2 shows the approach to the costochondral plate commonly used in securing a graft. In order to obtain a large graft two adjacent rib cartilages are resected en bloc. The



FIG. 9.—Case 6 (a) Squamous cell carcinoma of the ear. (b) Appearance after primary excision of tumor and suture of ear to the post-auricular skin. Following this step a patterned framework of tantalum mesh was inserted under the skin in the region of the aural defect. (c) After elevation of post-auricular skin and tantalum mesh and application of a skin graft to the post-auricular wound.

excision of a disc, 2 to 3 mm. in thickness, at the level of each transection makes easier the removal of such a block of cartilage. Inspection of such a graft from its posterior aspect shows (Fig. 3) that there is a concavity in the cartilaginous portion of the thoracic cage. This can be used effectively in the carving of cartilage for reconstruction of the ear. As the rib cartilage is split longitudinally, advantage is taken of the curling effect to exaggerate this concavity. Cartilaginous or fibro-muscular fusion of two adjacent cartilages is made use of in obtaining the desired width of graft. With attention to these details, it is possible to cut and carve, from costochondral cartilage, a free graft which has size, shape and rigidity, suitable for reconstruction of the external ear.

#### CASE REPORTS

**Case 1. Partial congenital absence of the external ear.** In this case as shown in Figure 4a, b, c, the microtia was corrected by the use of a cervical tubed pedicle. Reconstruction was carried out in three stages: the construction of the tubed pedicle of skin in the neck, the transfer of its distal end to the upper, anterior margin of the pinna, and the final division of the tubed pedicle with suture to the outer margin of the ear.



**Case 2.** *Partial congenital absence of the external ear.* In this case the operative steps were carried out as shown in Figure 5d. Transverse section of the rudimentary ear at the junction of its middle and upper thirds with rotation of the upper third anteriorly and suture of both segments to the skin of the mastoid area was done at the first operation. A free graft of carved cartilage was inserted as a wedge at the second operation. Elevation

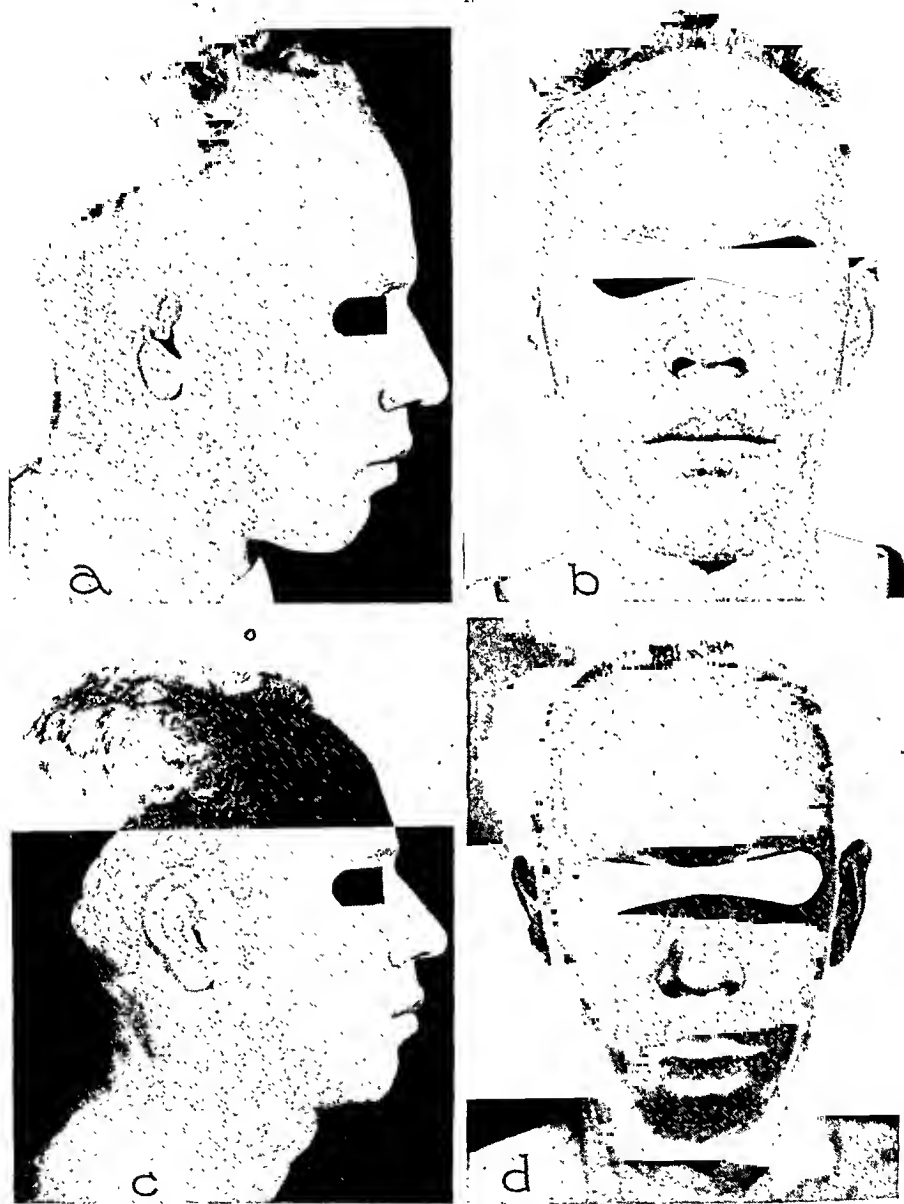


FIG. 10.—Case 7 (a and b) Traumatic loss of upper two-thirds of ear. (c and d) Appearance after reconstruction by use of carved cartilage and tubed pedicle from neck.

of the graft and backing with a split skin graft was done at the third operation. Minor revision of the tissue in the region of the helix is required before this reconstruction can be looked upon as completed. Photographs are shown in Figure 5 a, b, c.

**Case 3.** *Congenital absence of the external ear.* In this case (Fig. 6) the position of the rudiment of the ear was such that it was necessary to carve a graft from costal

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cartilage in the shape of the letter "C." This was embedded at the first operation. At the second step the cartilage was elevated from the head and a split skin graft was applied behind it. At a third operation the congenital remnant of ear cartilage was displaced behind the graft. This increased the lateral concavity to simulate a concha, provided rigidity to the constructed auricle and established the proper cephalo-auricular angle.

**Case 4. Congenital absence of the external ear.** In this case (Fig. 7) the small rudimentary ear was used only as a foundation for the reconstruction. Carved costal cartilage

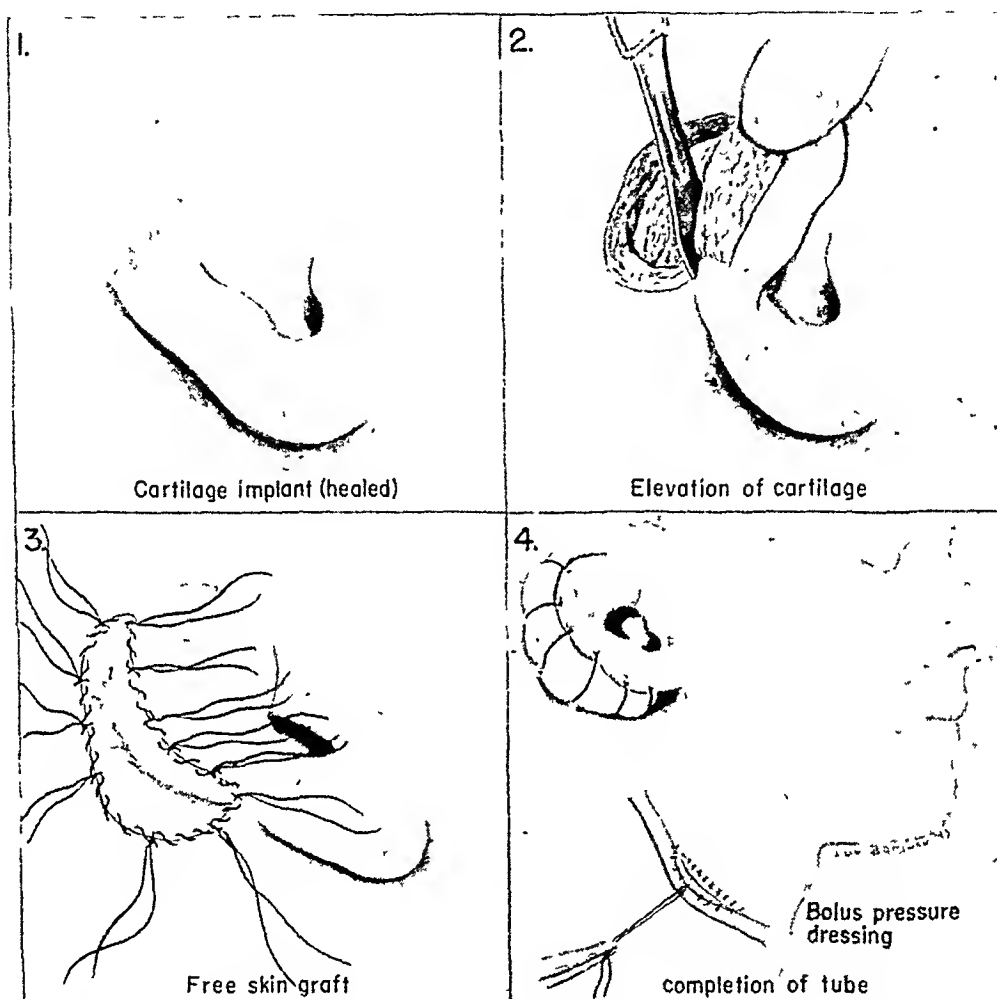


FIG. 10.—(e) Steps in elevation of implanted cartilage, backing with split skin graft and construction of tubed pedicle.

was buried in the auricular area at the first operation. At the second operation the cartilage was elevated from the head and a split skin graft was applied to the posterior aspect of the graft and to the defect of the aural and mastoid regions. Reconstruction was completed in two stages.

**Case 5. Congenital absence of the external ear.** Operative steps one and two in this case were the same as in Cases 3 and 4. The curling of the cartilage in this case was used to maximum effect in the simulation of the concha. (Fig. 8.) The associated facial asymmetry made the estimation of the required size of graft difficult to determine. Rather than disfigure the skin of the cervical region in this young girl, a tubed pedicle was constructed on the arm and transplanted to the ear in the reconstruction of the helix. This construction required three additional operative steps, five operations in all.

**Case 6. Loss of substance of the middle third of the ear by the surgical excision of malignant tumor.** This patient had a squamous cell carcinoma of the skin of the ear which

had invaded the auricular cartilage. At the time of excision the remainder of the ear was sutured to the post-auricular skin as shown in Figure 9. At the second operation a supporting framework of tantalum mesh was inserted under the post-auricular skin now in the middle third of the ear. At the third operation the constructed ear was elevated from the head and a split skin graft applied behind it.



FIG 11—Case 8 (a) Traumatic loss of upper half of ear (b) Appearance after implantation of carved cartilage. (c) Appearance after elevation of cartilage graft and application of a tubed pedicle to simulate the helix. (d) Front view after reconstruction.

*Case 7. Traumatic loss of upper two-thirds of external ear.* The patient lost the upper two-thirds of his ear in an injury in which he was thrown from a jeep. The ear was amputated by flying glass. Photographs are shown in Figure 10. Reconstruction was by the insertion of carved cartilage, its elevation and application of a skin graft posteriorly and the use of a cervical tubed pedicle to construct the helix. Visible defect

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of the scalp in the region of the cephalic portion of the skin graft was camouflaged by tattooing.

**Case 8.** *Traumatic loss of upper half of external ear.* This patient lost the upper half of his ear in an automobile accident. Photographs are shown in Figure 11. Reconstruction was carried out five years after the primary injury. Operative steps were the same as in Case 7.

**Case 9.** *Traumatic loss of upper half of external ear; reconstruction by recovery and implantation of autogenous auricular cartilage.* In an accident in which this patient was thrown from an automobile the upper half of the ear was amputated. The astute interest of a resident surgeon sent the relatives to another hospital where first aid treatment had



FIG. 12.—Case 9 (a) Traumatic loss of upper half of ear. (b) Appearance after reconstruction by use of autogenous auricular cartilage (see case report) and reproduction of appearance of helix by revision of soft tissue over the cartilage graft.

been given. The amputated ear was recovered from a basin of discarded dressings. It was washed with soap and water, sterilized with merthiolate solution. The skin was then removed and the auricular cartilage was buried in the abdominal wall. The lacerated ear was sutured to the skin of the mastoid area. Six weeks later the cartilage was removed and implanted behind the post-auricular skin. It was disappointing to note the excessive fibrosis around the cartilage. At subsequent operations the cartilage has been elevated from the head. Photographs are shown in Figure 12.

**Case 10.** *Congenital absence of the external ear.* In this case particular difficulty was encountered because the anomaly left only skin of the scalp in the aural region. After implantation of a large carved graft of cartilage there was excessive growth of scalp hair over the skin of the new ear. A tubed pedicle was used to construct the helix. Displaced hair of the scalp was removed by electrolysis.

### SUMMARY

Ten cases are reported in which partial or complete reconstruction of the external ear has been carried out. Reconstructions have been effected by the use of buried free grafts of cartilage, their elevation from the head and their backing by free grafts of skin at a second operation. A small tubed pedicle

has been used to effect the appearance of the helix in some cases. Technical details in the cutting and carving of costal cartilages have been set down. The opinion is advanced that reconstruction of the external ear, acceptable to patient and to surgeon, can be effected if attention is given to these details.

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## CHOLEDOCHUS CYST \*

### Case Report with Brief Comment

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THE GREAT RARITY of the condition known as choledochus cyst or idiopathic cystic dilatation of the common bile duct as judged by the paucity of reports in the literature, should make the report of a single case diagnosed preoperatively and successfully treated by primary anastomosis to the intestinal tract of some interest. Its relative infrequency is manifested by the fact that Judd and Greene<sup>5</sup> at the Mayo Clinic were able to find only one case despite a review of 17,381 biliary tract operations covering a period of 19 years. Likewise, Smith<sup>12</sup> at the Presbyterian Hospital in New York, collected only two choledochus cysts from 757,000 admissions to that institution. Numerous excellent reviews of the literature pertaining to this condition are to be found, notably those of McWhorter<sup>8</sup> in 1924, Zininger and Cash<sup>14</sup> in 1932, and, more recently, of Shallow *et al.*<sup>11</sup> in 1943. The latter group were able to collect only 175 cases, and Smith could find only 181 cases in the literature. McLaughlin<sup>7</sup> is of the opinion that the total number is certainly less than 200. According to Blocker *et al.*,<sup>2</sup> Lavenson credited Vater in 1723 with finding the first choledochus cyst. Clark<sup>4</sup> remarks that the first case report was made by Todd in 1817, and Saint<sup>10</sup> states that Neugebauer, in 1924, was the first to diagnose a case preoperatively. Since that time diagnosis still remains uncommon. Berkley<sup>1</sup> reported a diagnostic error of 98% in reviewing 53 cases. Many authors, particularly Zininger and Cash,<sup>14</sup> Morley<sup>9</sup> and Ladd and Gross,<sup>6</sup> feel that the high mortality associated with this condition results primarily from failure to recognize the true pathologic condition either preoperatively or at the time of surgery, and therefore failure to institute or an undue delay in instituting anastomosis between the intestine and the biliary tract. The etiology of this condition remains obscure, although many hypotheses have been advanced, practically all of them dealing with some developmental anomaly either of formation or of growth.<sup>9, 11, 14</sup>

#### CASE REPORT

E.R.S., Hospital No. 123963, 5-year-old white male, was first admitted to the Surgical Service of the Beckley Hospital on May 7, 1947, with the major complaints, as given by his mother, of intermittent abdominal pain, occasional slight jaundice, alcoholic stools, abdominal mass, low-grade fever, and episodes of nausea and vomiting, these symptoms having repeatedly occurred with increasing intensity since the age of two years.

*History of Present Illness and Previous Admissions.*—According to the mother, the patient was the fourth of five normally born children, and the first two years of his life had been quite uneventful. At the age of three, however, he began to complain occasionally of right upper quadrant pain, this being noticed most often following the ingestion of food. The pain was described as being cramplike, doubling the child up during the more severe episodes. At about the same time the mother observed that his skin and

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sclera were frequently yellow. The symptoms described above became more marked, and at about the age of four a mass was discovered in the right upper quadrant for the first time. The mother stated that the mass fluctuated considerably in size from day to day. Alcoholic stools began to be noticed, usually occurring following episodes of fever associated with enlargement of the mass and the appearance of jaundice. These symptoms continued, and he was first hospitalized on the Pediatric Service of this institution on May 13, 1946, when the abdomen was found to be distended and there was a large palpable mass in the right upper quadrant, the latter being interpreted as an enlarged gallbladder. His temperature was 100.4 on admission. Laboratory studies revealed a fragility test with no increase in hemolysis, an icterus index of 53, and a red blood count of 3.9 million with a hemoglobin of 56% (photoelectric); the white blood count was normal; the van den Bergh test showed a reaction of the immediate obstructive type; and urinalysis was negative except for a biliuria. A flat roentgen-ray film of the abdomen revealed what was thought to be a large mass in the right upper quadrant. A cholecystogram failed to reveal any gallbladder shadow, leading to the roentgenographic diagnosis of a probable pathologic gallbladder. On conservative therapy the jaundice declined and the fever subsided; and as these improved, his abdominal complaints disappeared. In view of his improvement the patient was discharged from the hospital, a diagnosis of acute catarrhal jaundice having been made.

Following discharge from the hospital, he was asymptomatic for approximately four weeks and then again began to have the same type of attacks. His mother noticed that the mass apparently was becoming larger very gradually and tended always to be present to some extent, even between acute episodes. On April 29, 1947, he was readmitted on the Pediatric Service for further study. At that time his temperature was 100.6, and he was clinically slightly icteric. A mass was present in the right upper quadrant, somewhat larger than on the previous admission and this time was interpreted as an enlarged liver. The mass was slightly tender on palpation. On this admission the icterus index was 23, and again the van den Bergh reaction was of the immediate obstructive type; urinalysis was negative; stool examination revealed no bile; red blood count was 4.36 million with a hemoglobin of 81% and a color index of .94; there was a leukocytosis of 15,500 with an essentially normal differential count. Again on symptomatic treatment he became afebrile and the mass in the right upper quadrant receded somewhat. He was discharged, a diagnosis of acute hepatitis having been made. He was readmitted to the hospital on the Surgical Service one week later for further investigation.

*Past Medical History.* Not remarkable.

*Previous Operations.* Uneventful tonsillectomy and adenoidectomy in October, 1946.

*Family History.* Irrelevant except for the fact that a paternal uncle died at the age of nine, reputedly with "yellow jaundice and gallstones."

*Physical Examination:*

*General Appearance.* On this admission the child was well nourished and well developed with a definite icteric tinge to the skin and the sclera. Temperature, 99.

*Head, eye, ear, nose and throat.* Negative.

*Lungs.* Clear to palpation, percussion and auscultation.

*Heart.* No arrhythmia, murmurs or enlargement were detected.

*Abdomen.* The superficial veins of the abdomen, as well as of the lower chest, were unusually prominent. The abdomen was slightly distended. A very large mass could be felt and seen in the upper abdomen extending approximately three fingerbreadths below the costal margin on the right and extending down somewhat less on the left. Beneath this mass on the right a second tumefaction could be felt extending well below the umbilicus and out into the right flank. The upper, larger mass was firm, moderately tender, and



was interpreted as liver. The lower mass had a cystic consistency and could be moved slightly, particularly in the transverse axis. The spleen was not palpable. Normal peristaltic sounds were heard on auscultation of the abdomen. No spasm or rebound tenderness were present. The costovertebral angles were negative.

*Rectal Examination.* Negative.

Remainder of physical examination negative.

*Laboratory Findings:*

*Blood.* Red blood count, 4 million with a hemoglobin of 80%; serology on two occasions, negative; clotting time, 4 min. 25 sec.; bleeding time, 1 min.; reticulocyte count, 1.5%; prothrombin time, normal.

*Blood Chemistry.* Admission icterus index, 35; urea nitrogen, 7 mg.%; fragility test revealed hemolysis beginning in a dilution of .34% and incomplete in a dilution of .26%; cephalin flocculation test, negative.

*Urinolysis.* Negative except for ++++ biliuria.

*Stool Examination.* Negative for bile.

*Roentgen-ray Findings:*

*Chest and Abdomen.* Flat film of the abdomen showed a great increase in density of the right upper and mid-abdomen. The lower half of the right kidney was outlined and was apparently of normal size, shape and position. From this film a roentgen-ray diagnosis of a large mass of the right upper and mid-abdomen was made. Roentgen-ray examination of the chest was negative.

*Intravenous Pyelogram.* No abnormalities of the urinary tract were visualized.

*Gastro-intestinal Series.* This showed marked displacement anteriorly and to the left of the first and second portions of the duodenum, apparently by a large extrinsic mass. Fourth-hour examination showed downward and medial displacement of the first portion of the transverse colon.

*Preoperative Course in the Hospital.*—The patient's temperature varied considerably during this period of observation, there almost always being slight fever, but recordings as high as 101 were made on several occasions. He was treated with glucose infusion, as well as a high-caloric, high-carbohydrate, and high-protein diet and was given large amounts of vitamin K daily. The low-grade jaundice varied considerably from day to day but subsided gradually, and the patient was icterus-free by the time surgery was performed. Episodes of severe abdominal pain occurred frequently, causing the child to cry bitterly. These attacks occurred most often immediately after meals. The cystic mass was found to change in size as much as 3-4 centimeters from day to day, a general regression in size occurring as his icterus subsided. Coincident with his general improvement and the decrease in icterus, one got the unmistakable impression that the mass had become much smaller.

A diagnosis of choledochus cyst was made and the patient prepared for laparotomy.

*Operation.*—Exploratory laparotomy; aspiration and biopsy of choledochus cyst; biopsy of liver; choledochocystoduodenostomy. (May 17, 1947.)

*Anesthesia.* Ether.

The abdomen was opened through a mid right-rectus incision. Upon opening the abdomen, the lower mass described previously was found to consist of a large, yellowish-tinged, tense, spherical, cystic structure covered with a veil-like layer of posterior peritoneum (see Figure 1). Just above this and extending bilaterally across the abdomen well beneath the costal margins, the diffusely enlarged liver could be seen, this apparently representing the firmer upper mass palpated preoperatively. The liver was of normal color but was somewhat granular in appearance. Jutting out from beneath the right margin of the liver and wedged between it and the cystic mass beneath was an extremely large, tense, thick-walled gallbladder, the latter appearing to be on top of the cyst. The duodenum had been greatly displaced and distorted and, instead of being in the usual

## CHOLEDOCHUS CYST

position, was actually extremely anterior and to the left of the midline. It was greatly flattened out and ribbonlike, being drawn tightly over the anteromedial aspect of the cyst and conforming to the contour of the latter. The pylorus was quite far anterior and was also displaced somewhat to the left. The right transverse colon had been displaced downward and the hepatic flexure, downward and mesially. Although fairly well fixed,

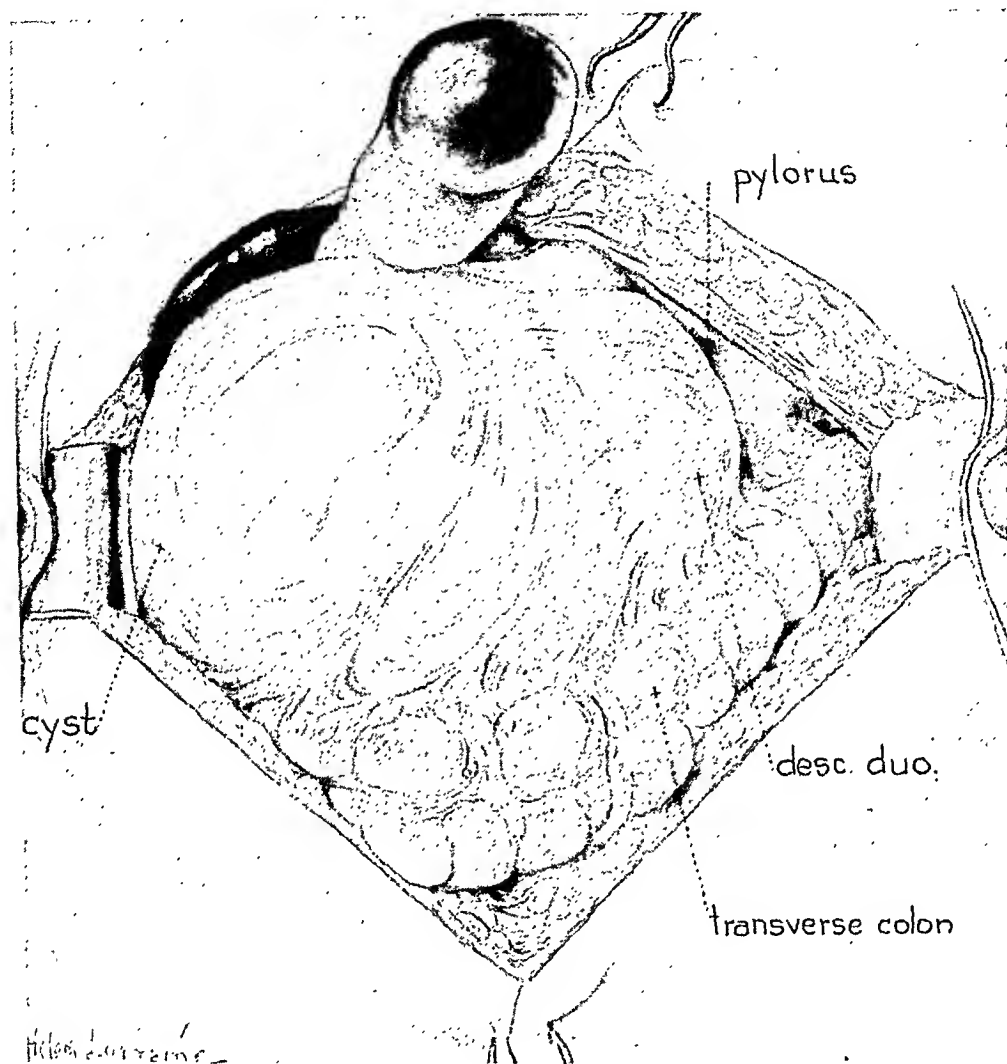


FIG. 1.—Artists' conception of the operative findings. The liver edge and the tense gallbladder can be seen beneath the right costal margin. The displacement of the transverse colon is also noted, as well as the marked anteromedial displacement of the duodenum and the pylorus.

the mass was found to be moderately movable in a transverse axis. The cystic duct was slightly enlarged in caliber and was found to empty into an apparently normal common hepatic duct just above the origin of the cystic mass. The common duct distal to the cyst appeared to be slightly enlarged on palpation but was otherwise negative. A number of soft hyperplastic lymph nodes were discovered in the region of the head of the pancreas, and there was a marked mesenteric lymphadenopathy. The small bowel was situated predominantly in the lower abdomen and to the left of the midline. Other than abnormalities resulting from displacement, the large and small intestines were negative. The head of the pancreas was displaced medially and anteriorly. The kidneys were normal in position and size on palpation, as was the spleen. Extensive dissection about the mass was not carried out nor were the extrahepatic biliary passages probed, inasmuch

as many previous authors have advised limited exploration once the operative diagnosis has been made in order to prevent unnecessary shock.

The posterior peritoneum overlying the cyst was incised, revealing the cyst wall to be quite thick. Using a tuberculin syringe and a hypodermic needle, several cubic centimeters of thin yellow bile were aspirated from the cyst. The abdomen was then carefully packed off with moist laparotomy pads and a trocar attached to a suction apparatus was introduced into the cyst. Seven hundred cubic centimeters of golden yellow bile were removed. A culture from this material was taken. Interestingly enough, as the bile was aspirated from the cyst, the gallbladder, which had previously been extremely tense, collapsed markedly. In view of the recommendations of other authors, notably Ladd and Gross, it was felt advisable to attempt immediate anastomosis between the cyst and duodenum without excision, either partial or total, of the former. The duodenum, because of its displacement, lay in an ideal position for a side-to-side anastomosis with the cyst. A biopsy of the cyst wall was obtained at this point, the wall being approximately 3 mm. in thickness, following which an anastomosis was effected. The stoma was situated in the first portion of the duodenum about one inch distal to the pylorus.

Following a complete change of gowns, gloves and drapes, a small biopsy was taken from the liver edge, the defect being closed with fine silk sutures. The wound was then closed in layers, using interrupted silk throughout.

During the operation the patient was given 500 cc. of whole citrated blood. He withstood the operation extremely well and returned to the ward in good condition.

*Postoperative Course.*—Almost immediately after operation the patient began to pursue a very stormy and hectic course. Unexplainable cyanosis was particularly troublesome during the first three or four days, making the administration of nasal oxygen imperative. Shortly after reacting from the anesthetic, the child began to vomit copious amounts of bile, necessitating the intermittent use of Wangenstein suction for seven or eight days. A marked tachycardia prevailed during most of the first postoperative week, and the temperature reached a peak of 102.6 on the fourth and fifth days; thereafter it began to subside. The skin sutures were removed from the wound on the sixth postoperative day, when the wound showed little evidence of normal healing. Abdominal pain was unusually severe and followed each attempt to take nourishment for many days. Parenteral supplementation consisting of Hartman's solution, 5% glucose, plasma, amigen, and blood were employed. Massive vitamin therapy, particularly large amounts of vitamin C and the B complex, and penicillin intramuscularly were also administered. Blood chloride on the third postoperative day was reported 525 mg.%. On the same day a red count was reported as 5.05 million with a hemoglobin of 112%, revealing some hemoconcentration. Moderate abdominal distention prevailed despite the use of the suction apparatus. On the eighth postoperative day, following a paroxysm of sudden vomiting, the wound disrupted throughout its entire length with eventration of small intestine. Sterile towels were immediately applied by the resident who was on the floor, and then the patient was taken to the operating room. His general condition was fair despite separation of the wound with protrusion of small intestine. A cannula was placed in the long saphenous vein, and he was given 250 cc. of plasma and the same amount of whole blood. It was noticed at the time of wound closure that the silk sutures were still intact, but there was no evidence of healing having occurred despite the postoperative administration of what had been thought to be adequate protein and large amounts of vitamin C. Following wound dehiscence with resultant evisceration, his course continued to be stormy, there being almost a persistent temperature to 100°. He gradually became able to take food, although for some weeks the ingestion of food caused some abdominal distention associated with cramplike abdominal pain. Normal-colored bowel movements were noticed on the tenth postoperative day. The silver wire sutures inserted at the time of secondary closure were removed on the twelfth postoperative day, when the wound had healed cleanly. Recovery of strength and weight was slow but progressive, and the

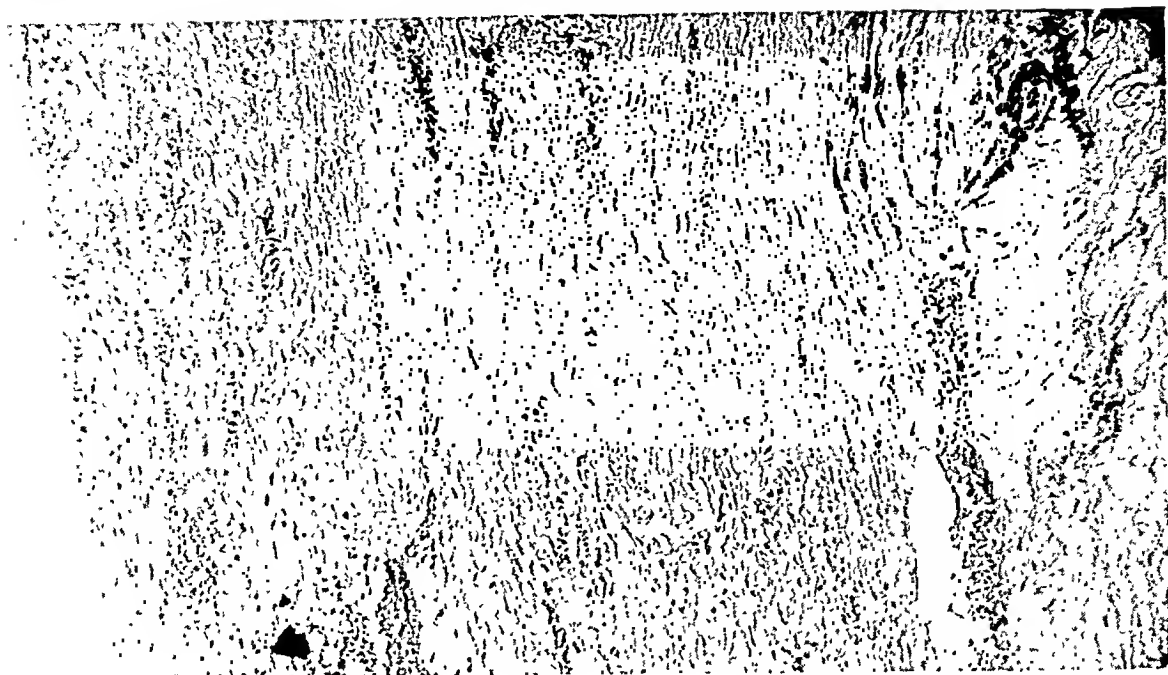


FIG. 2.—A photomicrograph of the cyst wall revealing the rather dense connective tissue and the lack of a definite lining membrane. (High power)

patient was discharged from the hospital on the twenty-seventh postoperative day asymptomatic and afebrile.

*Pathologic Examination.*—Microscopically the biopsy of the cyst wall was reported as showing moderately dense connective tissue which was relatively acellular and devoid of a proper lining (see Figure 2).

The biopsy of the liver histologically showed some excessive cellularity about the portal spaces and increased periportal fibrosis (see Figure 3).

The culture of the bile taken from the cyst revealed an almost pure growth of *Escherichia coli*.

*Follow-up.*—The patient was followed in the Outpatient Department for the first few weeks after discharge, his course for the most part being a steady improvement. Approximately six weeks after discharge from the hospital he experienced an episode suggestive of low-grade cholangitis, his mother stating that nausea, vomiting, temperature elevation, and a slightly icteric tinge to the sclera were noted. This attack, however, did not require hospitalization, his parents not even consulting the family physician, inasmuch as they had been warned before the child's discharge that such episodes might occur. He was last seen four months after operation, at which time he had gained approximately 5½ pounds and had been totally asymptomatic for two months.

#### COMMENT

The case presented would appear to be quite typical in practically all respects. The classical triad of mass, jaundice, and pain was present in this case, as were the less often emphasized symptoms of intermittent fever, occasional nausea and vomiting, and fluctuation in size of the mass. As would be expected, the findings characteristic of obstructive jaundice were present at the time the patient was admitted. Interestingly enough, as has been noted in the literature,<sup>3</sup> the condition had previously been diagnosed as acute catarrhal jaundice and, on a second admission, as acute hepatitis. McLaughlin<sup>7</sup> has remarked that an absolute preoperative diagnosis of choledochus cyst is impossible. However,



FIG. 3.—Photomicrograph of section of liver showing the increased cellularity about the portal spaces, as well as some increase in fibrosis. (Low power)

this case was considered to be such because of the typical and almost pathognomonic features of the case.

The surgical procedure carried out was that which apparently has been most generally recognized as giving the lowest mortality, namely, anastomosis of the cyst to the duodenum, which seems to us more accurately called choledochocystoduodenostomy than choledochoduodenostomy as in the past. Extensive dissection was not carried out, although more information could probably have been obtained by so doing. Inasmuch as most case reports, particularly those of Ladd and Gross,<sup>6</sup> have demonstrated that prolonged dissection has often resulted in high mortality, only enough exploration was done to confirm the preoperative impression. Although the immediate postoperative course was quite stormy and complicated by wound dehiscence with resultant evisceration, the patient at his last examination four months later was asymptomatic and had regained his preoperative weight of 43 pounds, his discharge weight being 37½ pounds. An episode resembling mild cholangitis occurred six weeks after operation, presumably from retrograde infection from the large cystic pouch.

Pathologic examination of the liver revealed some increased periportal cellularity and fibrosis, which in general conforms to the microscopic picture of the case reports in which liver biopsy was done,<sup>14</sup> although it was much less severe than in many. However, symptoms suggestive of marked liver involvement had subsided prior to the time of surgery. Examination of the cyst wall revealed a characteristic marked fibrosis with no evidence of a definitive lining membrane, this corresponding with most previous reports.<sup>6, 11, 14</sup> According to the literature, many different organisms have been cultured from the contents of the cyst.<sup>11, 13, 14</sup> *B. coli*, has often been found as was the case in this particular patient.

#### SUMMARY

A case of that unusual condition known as choledochus cyst diagnosed pre-operatively and apparently successfully treated by choledochocystoduodenostomy has been presented, as well as brief comments on its rarity and historical aspects. It is discussed briefly in the light of previously reported cases. Four months after operation the patient is asymptomatic, although initially he pursued a stormy course.

"The most recent check-up was made in June, 1948, at which time the patient was totally asymptomatic and weighed 48 pounds, this representing a weight gain of 10½ pounds over his discharge weight."

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# INTERNAL HERNIA WITH STRANGULATION OF BOWEL DUE TO A DEFECT IN THE FALCIFORM LIGAMENT \*

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LOS ANGELES, CAL.

ALTHOUGH THE REGION of the umbilicus is the site of a wide variety of congenital lesions, the occurrence of abnormalities in the underlying structures, i.e., the round and falciform ligaments of the liver, is indeed a rarity. Trimmingham and McDonald<sup>1</sup> have classified twelve different anomalies in the region of the umbilicus. They state: "The umbilical vessels converging at the umbilicus, persist, normally, as the two obliterated hypogastric arteries, and the ligamentum teres of the liver's falciform ligament. It is doubtful whether this process is ever subject to pathologic aberration." The author would like to present two cases of congenital defects in the liver's falciform ligament. In the first case, the defect in the falciform ligament was large and contained omentum. In the second case, the defect in the falciform ligament was small and contained a loop of ileum producing intestinal obstruction with strangulation.

The literature on intra-abdominal hernias is composed mainly of individual case reports, studies of limited groups of cases and reviews of special types of hernias. Moynihan<sup>2</sup>, in 1906, published an excellent review of the various peritoneal fossae and reviewed the cases of intra-abdominal hernias up to that time. Short<sup>3</sup> reviewed the cases reported between 1906 and 1915, and in 1925. Short<sup>4</sup> reviewed the literature. Hansmann and Morton,<sup>5</sup> in 1939, published the latest review on the subject.

The author believes that the following case reports are of unusual interest.

## CASE REPORTS

**Case 1:** I was called to see a 63-year-old white male who had severe pain in the umbilical region. He had been vomiting for several hours. His bowel movements were normal. The patient had been seen a few hours before by another physician who had made a diagnosis of gastroenteritis. Three years before, in another city, the patient had been jaundiced for two months. This was unaccompanied by abdominal pain or vomiting. Gall bladder roentgenograms had been taken, but the patient did not know the results.

Physical examination revealed no abnormalities of the chest. The abdomen moved with respiration and was soft on the left side. The whole right side of the abdomen was somewhat spastic with marked tenderness and rebound tenderness, more marked in the right upper quadrant than in the right lower quadrant. Rectal examination was negative.

The patient was hospitalized and had a temperature of 99.2°, pulse 120. Blood Count: Hemoglobin 109%. RBC. 6,050,000, WBC 17,000, neutrophils 88, lymphocytes 8, monocytes 4, shift to the left. Urine showed a trace of albumin and was faintly positive for bile. Upright roentgenogram of the abdomen showed no air under the diaphragm.

The patient was taken to surgery with a diagnosis of acute surgical abdomen (perforated peptic ulcer or acute cholecystitis). On entering the peritoneum, the omentum appeared to blanket all the viscera and seemed to be running in several directions. Up through the center of the omentum extended what looked like a "guy rope" to the

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## INTERNAL HERNIA

anterior abdominal wall. The disposition of the omentum appeared quite confusing, and only after dissecting it off the duodenum and gall bladder did the true situation become apparent. The fundus of the gall bladder was gangrenous and perforated, and had produced an intraperitoneal abscess which was walled off completely by the omentum. The omentum came up, as it usually does, to envelop the duodenum and gall bladder, but in addition, it had swung up around and through a large V shaped defect in the falciform ligament to again reach the duodenum and gall bladder. This "guy rope" piece of tissue was seen to be the obliterated umbilical vein, running from the porta hepatis to the umbilicus in the anterior abdominal wall, and the falciform ligament ended as a free edge, leaving a V shaped defect between the round and falciform ligaments. (see

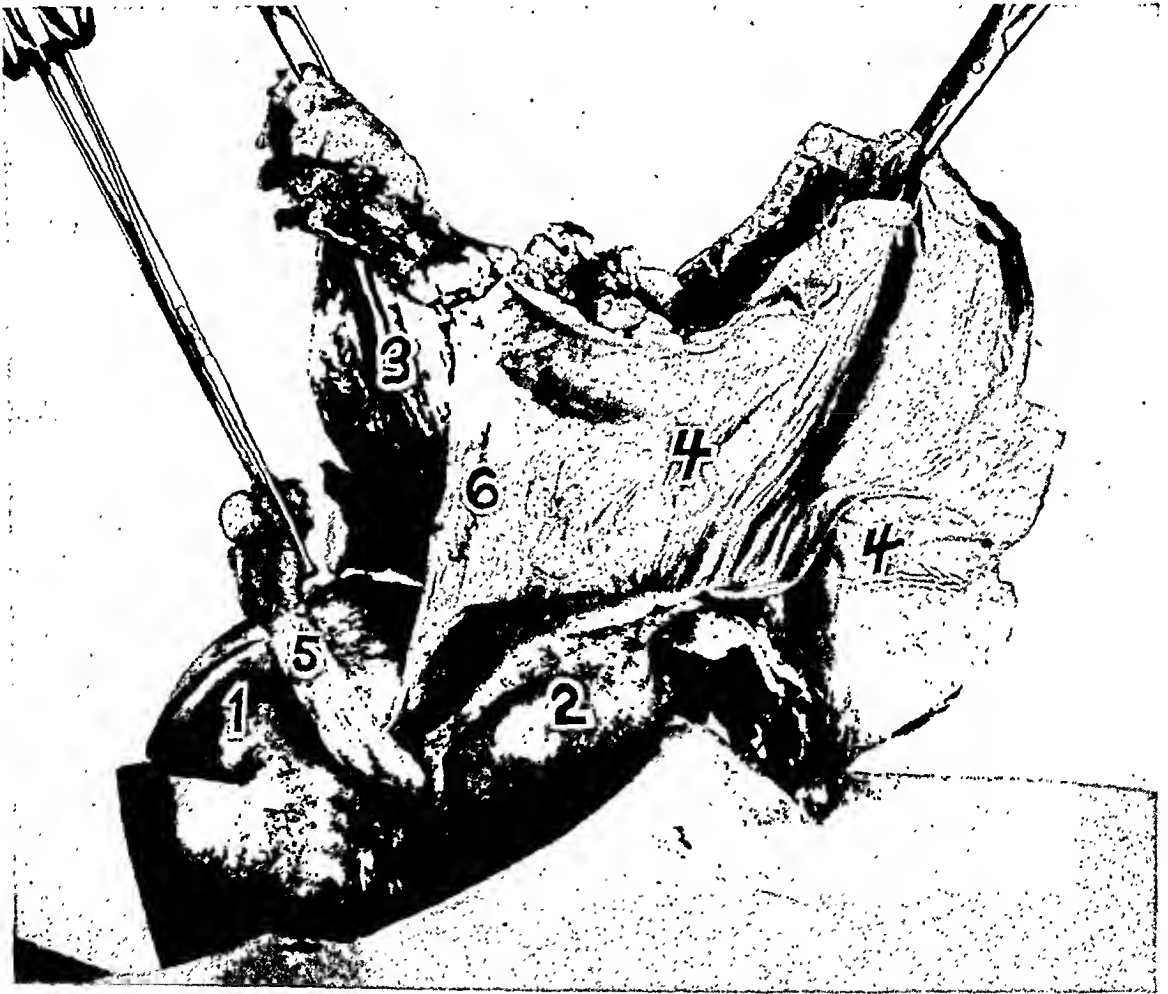


FIG. 1.—Anterior view of defect in falciform ligament with round ligament held up towards the anterior abdominal wall. (1) Right lobe of liver. (2) Left lobe of liver. (3) Parietal peritoneum covering undersurface of right leaf of diaphragm. (4) Parietal peritoneum covering undersurface of left leaf of diaphragm. (5) Round ligament. (6) Falciform ligament.

Fig. 1). No perforation was found in the gastro-intestinal tract. A cholecystostomy was done. The postoperative course was stormy and the patient died on the fourth postoperative day.

Autopsy revealed the described defect in the falciform ligament, associated with a lack of development of the left lobe of the liver, acute exacerbation of chronic cholecystitis with cholelithiasis, localized peritonitis, right retroperitoneal cellulitis, and coronary sclerosis.

Case 2: With the permission of Dr. Marcus H. Rabwin, Attending Surgeon at the Cedars of Lebanon Hospital, Los Angeles, I am presenting the following case which



occurred on his service. This patient had a similar defect in the falciform ligament with strangulation of the bowel.

A white male, 71 years of age, was admitted in a moribund condition and died in the hospital within a few hours, without operation. The patient gave a history of cramping, upper abdominal pain and vomiting for four days.

Examination revealed distention of the whole abdomen. Flat film of the abdomen

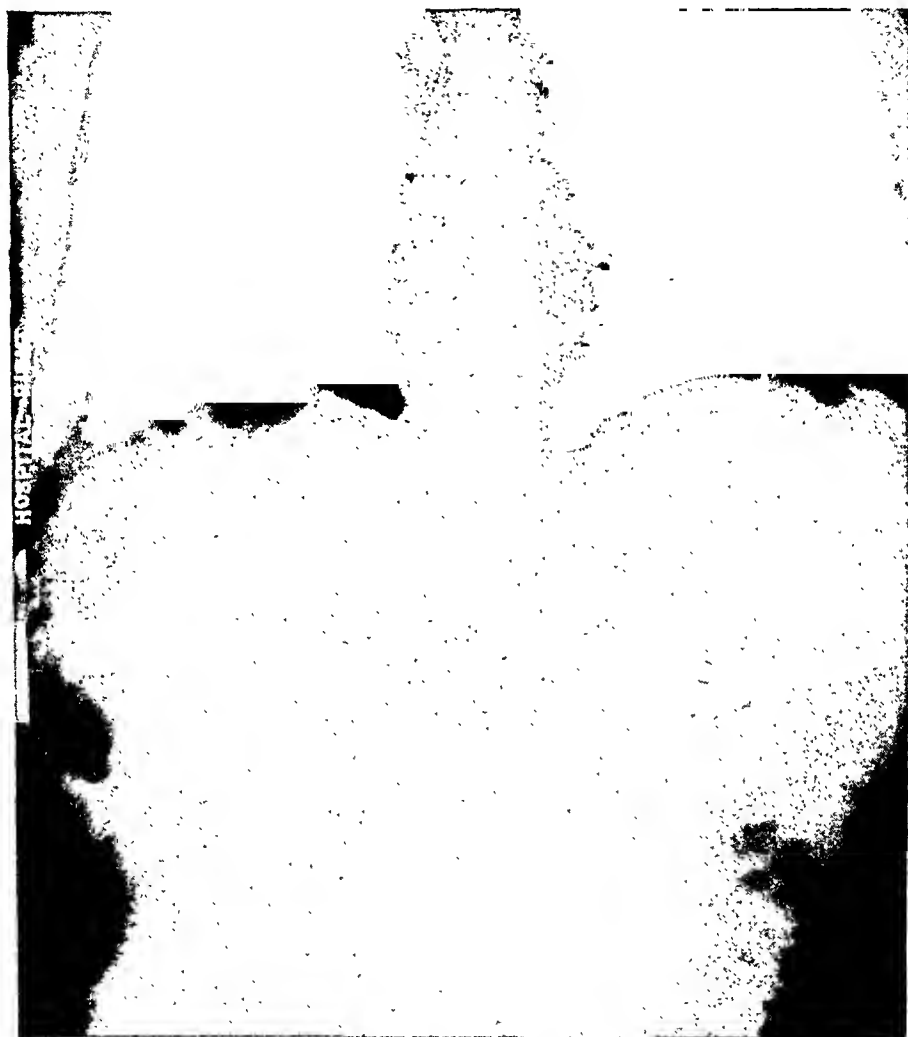


FIG. 2.—X-ray showing gas shadow in a closed loop of small intestine under right diaphragm. Also distended obstructed loops of small intestine down below.

revealed a gas shadow under the right diaphragm which was between the liver and diaphragm and was interpreted as free air.

At autopsy there was a loop of strangulated small intestine which had herniated itself through a defect in the falciform ligament. The cause of death was intestinal obstruction with strangulated bowel. After the autopsy, the flat film was reexamined and it became apparent that what looked like free air was actually a gas shadow in a closed loop of small intestine (see Fig. 2). Thus the diagnosis could have been made from this roentgenogram had we been aware of the existence of this rare condition.

DISCUSSION

A review of the literature discloses only one other report of an abnormality of this type. Schutz and Ziegler<sup>6</sup> report a case of intestinal obstruction due to internal hernia beneath the umbilical vein in a new born baby. The infant was operated on during the first week of life. At operation ten to twelve cm. of small intestine were found protruding through a small aperture just behind the ligamentum teres of the liver. The loop of intestine, as in our case, had entered the defect on the left side and had its exit on the right side, so that it again lay between the right lobe of the liver and the diaphragm.

Cullen<sup>7</sup> states that the peritoneum may be elevated over the umbilical vein in the form of a mesentery, but he makes no mention of an aperture between the vein and the anterior abdominal wall.

In one of the three cases, the defect in the falciform ligament was an incidental finding. Undoubtedly the occurrence of internal hernias is more frequent than one would think from the paucity of reports in the literature. This is so, because most of them exist without producing symptoms, just as patients frequently have asymptomatic external hernias. Alexander<sup>8</sup> has pointed out that internal hernias can be easily missed during a routine gastro-intestinal series. He advises observation of the small intestine at more frequent intervals by the radiologist. In the other two cases, the defect in the falciform ligament caused intestinal obstruction, and in one of these cases strangulation was also present.

Although internal hernias are uncommon they are important for the general surgeon because they may be met unexpectedly at the operating table. If the diagnosis could be made before operation, as shown in the photograph of the roentgenogram, it would be of vital importance.

Steinke<sup>9</sup> has classified internal hernias into three divisions: (1) Retroperitoneal (paraduodenal, paracecal, intersigmoid, supravesical and through the foramen of Winslow), (2) Intraperitoneal (anomalous openings in the mesentery, transverse mesocolon, omentum and broad ligament of the uterus), and (3) Postoperative after anterior or posterior gastroenterostomy and after the Baldy-Webster type of uterine suspension.

To the above classification, should be added a new group of internal hernias, i.e., hernias through defects in the falciform ligament. These defects undoubtedly are congenital anomalous openings and as such, should be included with internal hernias of the intraperitoneal type.

SUMMARY

1. Another group of internal hernias is added to the standard classification, i.e., hernias through defects in the falciform ligament.
2. The diagnosis may be made preoperatively.
3. An internal hernia is occasionally found as an incidental finding while operating for other conditions.
4. It is important to be familiar with internal hernias because it enables

the surgeon to recognize more quickly the condition at hand, and because reduction of the intestines can be effected with a cure.

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# ACUTE TORSION OF THE GALLBLADDER °

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## I. PURPOSE

The purpose of publishing this article on acute torsion of the gallbladder is to direct attention to an entity which is seldom mentioned in American medical literature, but which should be seen with increasing frequency in the future since it occurs predominantly in elderly people.

## II. HISTORICAL DATA

In 1898 Wendel<sup>14</sup> reported the first case in a 23-year-old female. Shipley's article in 1927<sup>12</sup> revealed the 21 cases of torsion of the gall bladder reported up to that time and added one of his own. This was the most exhaustive study at that period. Short and Paul's (1934) classical discussion<sup>13</sup> is the most outstanding, both in comprehensiveness and clarity. The authors feel that the time spent in reading this excellent work is indeed worthwhile. Meeker and Lisenby's<sup>11</sup> recent work is especially desirable because of the beautiful plates depicting anomalies of the gallbladder.

## III. INCIDENCE

As late as 1946 there were only 76 cases reported in the literature available.<sup>5, 6</sup> All reports indicated that the condition is found more frequently in females of the older age group, particularly of the viscerotopic type. According to Short and Paul,<sup>13</sup> 7 to 8% were males. The age of incidence varied from 11 years to 83 years. The vast majority, however, were between 60 and 80 years.

## IV. MECHANISM OF TORSION

Four possible anatomic arrangements of the viscus are mentioned, only the fourth of which is important in our discussion:

1. Gallbladder may be embedded in the liver tissue.
2. Gallbladder may be closely attached to the under surface of the liver, with intervening connective tissue.
3. The outer surface of the fundus may be surrounded by peritoneum and the rest attached to the liver, but not actually touching because of the interposed fibrous tissue (the normal arrangement).
4. Gallbladder may be completely surrounded by peritoneum, and be free, except where it is attached to the cystic duct.

With the arrangement described in No. 4 above, it is conceivable that the

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cause of torsion is related to the movement of normal peristalsis in the transverse colon. As peristalsis proceeds, the overlying gall bladder becomes twisted. The associated abdominal rigidity aggravates the existing condition.

The matter of torsion, either clockwise or counter-clockwise, is still unsettled and is not important. The loss of elasticity of supporting structures is probably a factor, particularly in the old age group. The volvulus is more liable to reduce itself in a younger person because elasticity is still present. Stones do not seem to be a predisposing factor and are only present in a moderate percentage of the cases studied.

#### V. SIGNS AND SYMPTOMS

In the majority of cases the onset is acute, with sudden, severe pain in the right upper quadrant, or midabdominal pain which may radiate to the back or shoulder and in other characteristics simulate a biliary colic. Vomiting is a frequent, but not constant, finding.

In more than half of the cases reported it was stated that a palpable tumor mass could be felt in the region of the gallbladder shortly after the onset of pain (within two hours). This mass is usually exquisitely tender, can be seen or felt more readily with respiration, and is associated with rigidity and spasm of the abdominal muscles. Muscle spasm and rigidity of the abdominal wall increase with the duration of the symptoms. Jaundice is rarely present; in fact it was not mentioned in any case reported.

When the volvulus is incomplete the onset may be insidious, with less pronounced symptoms. Such cases are extremely difficult diagnostic problems because of their similarity to acute cholecystitis. Cases have been reported where the individual had severe pain and a palpable mass, both of which disappeared only to recur at a later time. Such a history should suggest the diagnosis of torsion.

Chills and fever are characteristically lacking. In fact, during the first 24 to 48 hours the temperature, pulse, and respiration are usually normal, but later all three may show a marked rise if surgical intervention is delayed.

Symptoms of peritonitis appear when the gallbladder becomes gangrenous and perforates. In only two reported cases has shock played a predominant role, and in one of these it was the apparent cause of death.

Flatulent indigestion, suggesting gallbladder disease, occurs infrequently in these individuals.

#### VI. DIFFERENTIAL DIAGNOSIS

Torsion of the gallbladder is most frequently diagnosed as cholecystitis or cholelithiasis, with hydrops or empyema of the gallbladder. Appendicitis, intestinal obstruction, twisted ovarian cyst, ruptured peptic ulcer have all been confused with this entity. However, in most instances, if the condition described herein is given consideration, diagnosis may not be too difficult.

Typically, torsion of the gallbladder occurs in an elderly viscerotonic female. The most striking symptoms are the sudden onset of severe epigastric pain (upper right quadrant), and the appearance of a palpable, tender mass a

short time later. The absence of jaundice, and constitutional symptoms such as fever, increased pulse and respiration, should suggest the diagnosis, especially if rigidity and tenderness are present on abdominal examination. Subsidence of the symptoms may occur if the volvulus becomes untwisted and the mass disappears. Likewise, the pain may be temporarily alleviated by manipulation of the tender mass, or by the assumption of various positions.

#### VII. PROGNOSIS

Hugh Arthur<sup>2</sup> mentions the mortality rate in cases of torsion as 16%. This could be reduced, however, providing an early diagnosis of the condition is made, since the chances for a successful operation and an early convalescence are excellent. All cases reported as having a fatal outcome either had perforated, expired from surgery, or were unrecognized on initial diagnosis.

#### VIII. TREATMENT

Early surgery will save the vast majority of cases recognized as torsion. The surgeon feels that a paramedian incision is the one of choice inasmuch as the tissue is loose and there is no difficulty in exposure. The cholecystectomy is simple but the general laxity of the tissues should make one extremely cautious, particularly in identifying the cystic and common bile ducts. One case of fatal outcome was caused by tying off the common bile duct. A few cases were reported to have had bloody drainage in the gallbladder fossa or peritoneal area. Early ambulation is essential.

#### IX. REPORT OF A CASE

The patient, R. P., a thin, 63-year-old white male, occupation—butcher, was first seen on 10/20/47. While at work three days previously, at 11:30 A. M., he was seized with a severe peri-umbilical pain associated with sweating and a feeling of faintness. The pain persisted without radiation; it was greatly aggravated by change of position and by coughing.

The evening of onset the patient vomited six or eight times, but this ceased the following morning and did not recur. The patient remained on a liquid diet throughout his illness, however. No belching, gas, distention, or bowel movements had occurred since two days prior to the onset of the present illness. There were no chills or fever, nor was there any jaundice. Pain, however, persisted.

In the past, the patient had had no similar episodes. However, at one time, about 30 years previously he had been treated for "ulcers"; these responded to a medical regime without recurrence. A review of systems, past health and family history did not reveal anything of note.

*Physical examination.* A tall, thin, 63-year-old white male, acutely ill, complaining of peri-umbilical pain; B.P. 120/76, pulse 78, resp. 18, temp. 99. The general physical examination was negative except for the abdomen, which on inspection presented a smooth, pear-sized mass, 1" above the umbilicus, and to the right of the mid-line. This mass moved with respiration, and with the patient turned on his left side it could be seen and felt across the mid-line to the left epigastric region.

The mass was exquisitely tender to palpation and could not be well outlined because of the associated rigidity of the abdominal wall. At times it appeared to pulsate, but with the patient in knee-chest position no pulsation was evident. In this position, however, manipulation of the mass gave temporary relief of the pain, with recurrence of its former severity as soon as the recumbent position was resumed.

The patient was seen in consultation several hours later (90 hours after onset of

present illness), at which time the temperature was 100.2, pulse 106, respiration 24. The physical findings otherwise were essentially the same as on previous examination except for more extensive tenderness and rigidity. The impression was acute abdomen, probably a ruptured ulcer. The laboratory studies were as follows:

Roentgen-ray—flat plate of abdomen: normal except for a ptosis of right kidney

Urine—negative

White count—16,000; polys, 85; lymph, 15

*Surgery.* With the aid of a pontocaine anesthesia, the abdomen was opened, using a paramedian incision. A dark, shiny gallbladder presented itself and was attached only at the cystic duct; the neck of the gallbladder was twisted 360 degrees. The common bile duct was readily identified. No bloody drainage was present. The gallbladder was excised between two Moynihan clamps and the stump doubly ligated; the abdomen was closed without drainage. The patient was made ambulatory 12 hours later. Convalescence was smooth except for a cigarette cough. Sutures were removed on the eighth day. Patient returned for a 30-day checkup and was found fit.

*Pathologic report.* 1. Gross: Gall bladder measure, 8×4 cm. It is reddish black in color and appears entirely gangrenous.

2. Microscopic: Almost complete hemorrhagic infarction. One medium-sized artery contains an organizing thrombus and all the veins are enormously dilated and plugged with blood. One section shows extensive old chronic inflammation and fibrosis accompanied by marked glandular infiltration into the wall. This infiltration is in the form of strands and the epithelial changes are the result of chronic inflammation.

#### SUMMARY

A case of torsion of the gallbladder has been presented. A patient having a history of acute pain in the upper right quadrant, followed by an abdominal mass within two to three hours and a gallbladder syndrome, should make one consider this possibility, particularly in an elderly viscerotomic male or female. The authors hope the paper may be of some assistance in establishing such a diagnosis.

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# SADDLE EMBOLUS OF THE AORTA

## Report of Successful Embolectomy\* †

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THE PURPOSE OF THIS PAPER IS to report an additional successful embolectomy at the bifurcation of the aorta. Although the literature of recent years<sup>1, 2, 3, 4</sup> records an increasing number of successful embolectomies for saddle embolus at this point, the total remains small. It is believed that the details of single case histories may still be of sufficient interest to justify a report of this kind.

### CASE REPORT

Mrs. C. C., a 52-year-old housewife who had been confined to bed for several weeks, was recovering from her second episode of cardiac decompensation, during which she had received digitalis. Auricular fibrillation was present. Late in February, 1946, the patient noticed vague pain in the anterolateral part of the left leg. This was followed by weakness in the peroneal group of muscles and by a mild foot drop. About ten days later, on March 4, 1946, while the patient was out of bed to the bathroom, there was rapid onset of numbness in both legs, followed by pain in the lower abdomen and sacral region which moved downward gradually to involve both legs. At this time, the patient became unable to walk and paralysis of the lower legs was soon complete. A physician administered morphine,  $\frac{1}{4}$  gr., without significant relief, while arranging for the patient's admission to Little Company of Mary Hospital.

The essential findings on admission were pain, coldness, numbness and paralysis of the legs, and diffuse pain in the lower abdomen and sacral region. The oral temperature was 96° F. Auricular fibrillation was present. The cardiac rate determined at the apex was 180 per minute. The pulse rate at the wrist was 80 per minute. The blood pressure in the left arm was 170/110 mm. Hg. Pulsation of the abdominal aorta could be felt distinctly almost to the region of the sacral promontory, but there were no pulsations below this point except for a weak pulsation in the region of the left femoral artery. This latter finding was interpreted as representing pulsation transmitted by a tail thrombus. A diagnosis of saddle embolus at the bifurcation of the aorta was made. Immediate embolectomy was advised.

Six hours after embolism, operation was performed. Under satisfactory general anesthesia, the bifurcation of the aorta was exposed transperitoneally through a midline incision which extended about equidistant above and below the umbilicus. (Fig. 3.) Pulsation in the aorta was present to within 2.5 cm. of the bifurcation. Below this point, a soft mass extending into both iliac arteries could be palpated through the walls of the vessels. The overlying peritoneum was divided, and the aorta and the iliac arteries in the region of the bifurcation were freed from the surrounding areolar tissue. Tapes were placed about the aorta and the iliac vessels, and an incision about 2 cm. long was made into the anterolateral portion of the vascular wall at the junction of the aorta and the right common iliac artery. (Fig. 1.) The obstructing mass of clot was removed from the region of the bifurcation, together with a tail thrombus about 6 inches long from the the right iliac artery. (Fig. 2.) The clot was removed from the left iliac artery in several pieces and free bleeding occurred with the force expected as each tape was released inde-

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pendently. The opening in the vessel was closed by a running mattress suture of fine "arterial" silk which everted the edges, producing intima-to-intima contact (Fig. 1), and at this time the intravenous administration of 10 cc. (100 mg.) heparin solution in 500 cc. normal saline solution was begun. The abdomen was closed. The patient's general condition was considered fair, the blood pressure having fallen from 140/80 to 110/60 during the operation, while the pulse rate varied from 100 to 140 per minute. The operation lasted 115 minutes.

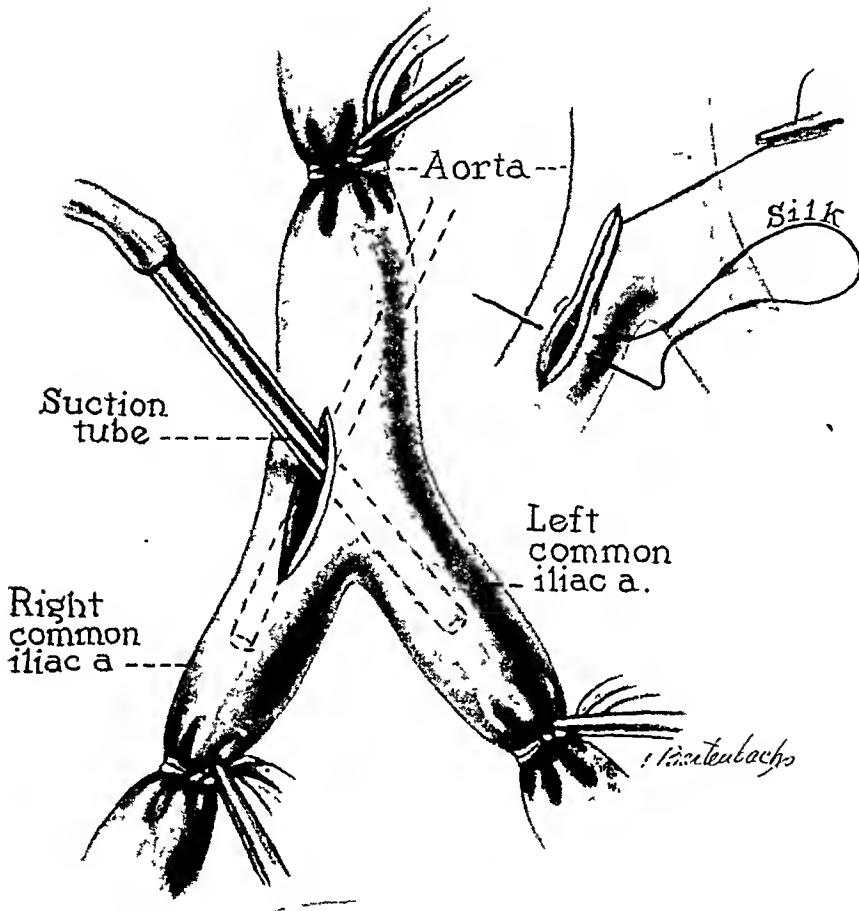


FIG. 1.—The incision in the vessel wall at the junction of the aorta and the right iliac artery is shown. By opening the vessel at this point, the mass of clot accumulated at the bifurcation was easily removed and it was possible to pass a suction tube into both iliac arteries. The tapes maintained hemostasis satisfactorily and apparently did not damage the vessel walls. In closing the incision, a single running mattress suture of 5-0 silk provided intima-to-intima approximation.

Immediately after the operation, pulsations could be felt in all peripheral arteries except the dorsalis pedis on the left. On the following day, paralysis of the peroneal group of muscles on the left was found to be present. The postoperative course was otherwise satisfactory. On the 5th day following operation, pulsation returned in the dorsalis pedis artery on the left, but marked weakness persisted in the peroneal group of muscles for about four weeks. Adjunct treatment consisted of novacaine injection of the lumbar sympathetic fibers bilaterally on the first postoperative day, spinal anesthesia (pontocaine

hydrochloride) on the second, third, fourth and sixth postoperative days, intermittent venous constriction, and anticoagulant therapy. The patient was allowed to be out of bed on the 12th postoperative day and was dismissed from the hospital 5 days later. Dependent edema of the left leg was present for about 6 weeks following the operation (Fig. 3), but was easily controlled by elastic bandages and has not recurred. During the summer of 1946, the patient enjoyed a 4,000-mile motor trip with her family. She has resumed and continued light household duties. Mild weakness of the peroneal muscles on the left persists. In the 23 months which have elapsed since operation, the heart disease has remained compensated. Fibrillation, however, is still present.

#### DISCUSSION

Embolic occlusion of any of the major arteries is not only a serious condition *per se*; it also indicates the presence of major underlying disease. The source of the emboli is most often the heart. Rheumatic endocarditis, particularly with mitral stenosis, and upon which have been superimposed the factors of infection, operative trauma, fibrillation, or coronary occlusion, is the most frequently

encountered basic pathology. Murray<sup>5</sup> states that in coronary disease the mural thrombus may attain such size that portions of it are not firmly attached and can be swept into the circulation. Far less commonly, vegetations from heart valves, atheromatous plaques from the aorta, or the unusual paradoxical embolus arising in the course of venous thrombosis<sup>6, 7, 8</sup>, cause embolic obstruction in the major arteries. Changes in the clotting mechanism associated with intensive or excessive digitalis dosage, as described by De Takats et al,<sup>9</sup> must be included in the etiologic background. Murray<sup>5</sup> and Reynolds and Jirka<sup>10</sup> have called attention to the influence of changes in cardiac rate and rhythm in dislodging emboli.

Thus, the onset of fibrillation or the restoration of normal rate and rhythm are often associated with embolism.

Obstruction at the bifurcation of the aorta due to a saddle embolus is the most serious of all peripheral embolic disturbances and, fortunately, the least common, comprising approximately 4.5 per cent, according to Pratt.<sup>11</sup> However, De Takats' compilation<sup>12</sup> of the figures given by Heidrich,<sup>13</sup> Petitpierre<sup>14</sup> and Pearse<sup>15</sup> places the incidence of saddle embolus at 10.14 per cent.

The patient with obstruction of the artery to an extremity, if untreated, may develop gangrene and survive subsequent amputation. It is generally conceded, however, that in every instance of aortic embolus obstructing the



FIG. 2.—The clot as assembled after removal. The tail thrombus is from the right iliac artery and was approximately 15 cm. long. The clot from the left iliac artery was removed in several pieces.

bifurcation in which the circulation is not restored, the patient is doomed to death from gangrene.<sup>5, 12</sup> The extremely rare reports in the literature<sup>16, 17</sup> which describe spontaneous recoveries of patients with saddle emboli of the aorta may concern partial occlusion with subsequent thrombosis occurring in such a manner as to permit the collateral circulation to become adequate. Another explanation may be the occurrence of simultaneous or almost simultaneous bilateral iliac or femoral emboli. Thus, in Reich's<sup>16</sup> case of aortic obstruction with recovery under conservative management, the patient had pain in hips and legs but no abdominal pain. It is not stated that both femoral pulsations were absent. The patient showed considerable improvement on the second day. Herrman's<sup>17</sup> case, diagnosed as saddle embolus of the aorta, had pain first behind one knee and, several hours later, behind the other knee. He had "fleeting pain in the abdomen and precordium." The femoral pulsation, barely palpable on the left, was not definitely palpable on the right.

#### DIAGNOSIS

The onset of persistent peripheral circulatory disturbances of severe degree in a patient whose medical background contains any of the above-mentioned etiologic factors should, until proved otherwise, warrant a diagnosis of peripheral arterial occlusion. The visual conception of the speed of arterial blood flow and the sudden arrival of an embolus at a point in the vascular system so narrow as to be completely blocked by the embolus make it easy to believe that the onset of symptoms (in peripheral arterial embolus) must be sudden. However, two general types of histories have been obtained in proven cases. One of these is characterized by sudden localized pain indicating approximately the point at which the embolus has been arrested and, after an interval lasting up to several hours, a diffuse type of aching pain throughout the areas distal to the obstruction, due principally to anoxia of the muscle and varying in degree with the amount of muscle involved. This clinical picture is ascribed to obstruction of the main artery, accompanied by vasospasm to a small degree proximal to the embolus, but principally distal, with subsequent thrombus formation blocking the collateral circulation. This sort of clinical picture is present in approximately two-thirds of the reported cases of peripheral arterial embolus.<sup>3, 5, 18</sup> It appears to be even more frequent in saddle embolus of the aorta, according to the review of



FIG. 3.—This photograph was taken a short time after dismissal from the hospital. The wound is healed solidly. The swelling of the lower part of the left leg can be seen. There was no significant difference in color or skin temperature of the right and left legs.

McClure and Harkins,<sup>2</sup> who found it present in 97 per cent of the cases reported by Hesse.<sup>10</sup> The other mode of onset seen in the remaining third of reported cases of peripheral arterial embolus is characterized by paresthesia as the initial symptom, followed by numbness, diffuse pain and paralysis as anoxia becomes more severe. The case reported herein and those reported by Ravdin<sup>20</sup> and Linton<sup>3</sup> had this type of history.

Murray,<sup>5</sup> in commenting on the difference in the symptomatology, pointed out that the smaller arteries near the periphery have a greater proportion of smooth muscle in their walls than do the larger central vessels and, therefore, may be the site of more severe vasospasm and pain. He states that in his cases of aortic and iliac emboli the pain at the onset was not as severe as in some of the more peripherally located emboli. Agar's patient,<sup>4</sup> treated successfully by embolectomy for saddle embolus at the aortic bifurcation, complained only of numbness followed by "discomfort." With relatively less smooth muscle in the larger vessels, there should be less vasospasm and hence less pain. For the same reason, one would expect less pain at the onset in patients whose vessels have atheromatous changes. The complete absence of pain as reported by de Takats<sup>21</sup> could be explained on the basis of one of these factors plus ischemia, which brought about an early physiologic block of sensory nerves.

According to Murray,<sup>5</sup> the absence of pulsations is the most important sign; yet, this finding is subject to careful consideration and analysis. Vasospasm may be so severe as to obliterate pulsations in vessels not obstructed by clot, as reported by Atlas<sup>22</sup> and by Reynolds and Jirka.<sup>10</sup> In these instances, the pulses may return while preparations for operation are being made. It must be concluded in these cases that an embolus has moved distally or that vasospasm has subsided. On the other hand, the presence of pulsations may be deceiving. Theoretically, the transmission of pulsations by a tail thrombus should produce a linear thrust (Nordentoft's sign) instead of an expansile type of pulsation, but this distinction may be difficult in the presence of much subcutaneous tissue. If the patient is not too obese, pulsations can be felt in the aorta above the embolus. The clearly defined point beyond which they are not palpable is often striking.

Tenderness at the site of embolus is not present early, but depends on the development of inflammatory changes in the intima. The color changes in the skin are important. Pallor and blanching occur early; later, mottled cyanosis appears. Leriche<sup>23</sup> has called attention recently to "marbled" blanching which, he warns, means complete arterial obstruction. He states that antispasmodic drugs and blocking of the sympathetic fibers are insufficient to restore the circulation at this stage and that surgical intervention is imperative. Later manifestations include motor and sensory paralysis, as ischemia produces a physiologic interruption of nerve and muscle function.

With the etiologic factors and symptomatology in mind, it would seem almost impossible to confuse the clinical picture of aortic embolus with the more gradual process of aortic thrombosis. In the latter, there are usually

weeks or months of development characterized by fatigability of the lower extremities, intermittent claudication, coldness of the feet, atrophy of the calves and thighs and, in males, impotence.<sup>24</sup> Most of Greenfield's patients<sup>25</sup> were seriously ill with some systemic disease or already had complications of their heart disease. However, in cases of thrombosis the circulation may become inadequate rather suddenly (in 10 per cent of cases, according to McKechnie and Allen<sup>18</sup>), and the onset of pain and evidences of circulatory inadequacy may therefore appear to be an acute and recent process. The differentiation should be made easily on the basis of the past history, the atrophy of the legs, and sclerosis of peripheral and retinal vessels. In many instances, roentgen-ray examination will show calcium deposits in the peripheral vessels.

Phlebothrombosis, characterized by pain and coldness and accompanied by sufficient vasospasm to obliterate palpable pulsations, might be confused with arterial occlusion, but it is unlikely that both extremities would be involved simultaneously. Furthermore, the events leading up to it, the lack of etiologic background for an embolus, its unilaterality, and the continued presence of sensation and voluntary motion should enable one to make the distinction.

#### TREATMENT

Embolectomy is the only life-saving treatment for a patient with an aortic embolus. Even in poor risk patients it is well to remember that they do not die from the operation of embolectomy: they die of gangrene, heart disease, or as a result of amputation. As a general rule, the sooner embolectomy is done, the better will be the results. Furthermore, as Pratt states,<sup>11</sup> thrombosis follows embolus in 50 per cent of cases and will spread to involve collateral vessels. This is one of the main reasons for early operation.

Morphine given for the pain will generally serve as the pre-anesthetic medication, with the addition of scopolamine or atropine. Two approaches have been used: one, a direct attack by exposing the bifurcation of the aorta,<sup>1, 3</sup> and the other, an indirect approach in which the iliac or femoral arteries are exposed and the clot dislodged by the retroperitoneal milking of Nyström<sup>26</sup> or by intravascular probing.<sup>10, 20, 27</sup> In the indirect methods, the clots are swept down by the pressure of blood behind them and removed from the vessels at or near the inguinal ligaments.

*The general condition of the patient will be the deciding factor in the choice of operative procedure.* There will be patients who are obviously extremely poor risks for the transabdominal approach and whose only hope lies in the success of the indirect removal of the clot. If the general condition of the patient warrants the abdominal approach, it appears to be a matter of choice whether one opens the peritoneum or not. Murray<sup>1</sup> finds the retroperitoneal approach entirely satisfactory. The time necessary to do the retroperitoneal dissection is probably about the same as that needed to close the peritoneum when the transperitoneal approach is used. Since the bowel is packed out of the way and need not be disturbed throughout the operation by the transperitoneal route, there should be little trauma to cause postoperative ileus; whereas it is well known that troublesome ileus may result from retroperitoneal dissection. A

special indication for the retroperitoneal approach might be the presence of intraperitoneal infection or suppuration. In such a case reported by Schmorell,<sup>28</sup> in which a saddle embolus of the aorta occurred in the presence of peritonitis following operation for appendicitis, the extraperitoneal milking method of Nyström was employed successfully.

Anesthesia will depend on the approach. The indirect approach through the femoral vessels can be made largely under local anesthesia. For the trans-abdominal route or for the deeper portion of the retroperitoneal milking skillfully given general anesthesia supplying adequate oxygen with the anesthetic agent is preferred. Two objections to spinal anesthesia have been expressed. One is that the relaxation it brings about in the vessels may allow the embolus to migrate, and it does not necessarily follow that it will go to a more accessible point. The other objection is that often there may be a fall in blood pressure with the spinal anesthetic contributing to the stagnation of blood and enhancing the chances of thrombus formation. However, Agar's successful case<sup>4</sup> was performed under spinal anesthesia.

The next point to consider is the method by which the lumina of the aorta and the iliac vessels are temporarily occluded. If the walls of the aorta and the iliac arteries are normal or, at least, not atheromatous, occlusion by the use of umbilical tape, clamping it close to the vessels and twisting the clamp, as apparently has been done in most of the reported cases, appears to be entirely satisfactory. The use of modified Moynihan intestinal clamps, as used by Gross in aortic resection for coarctation,<sup>29</sup> and the Bethune clamp, as recommended by Linton,<sup>3</sup> would cause less wrinkling of the intima and, perhaps for that reason, less chance of disrupting it.

There are few references in the literature describing the incision in the aorta.<sup>3, 5</sup> The anterolateral incision at the junction of the aorta and the right common iliac artery, as shown in Figure 1, is entirely satisfactory. In addition to providing adequate room for removal of the mass of clot at the bifurcation, it permits the introduction of a suction tube into both iliac arteries for the removal of any clot which has not adhered to the main mass. The incision in the vessel wall is about 2 cm. to 2.5 cm. long. It is believed that a smaller incision would necessitate breaking up the mass of clot, thus running the risk of a small piece being overlooked and swept distally on re-establishment of the circulation.

Usually it is not difficult to remove the clot resting at the bifurcation of the aorta. If this is done before clotting has occurred in the collaterals, a single tail clot (Figure 2) will come with it. However, if the clot becomes fragmented, suction by means of a glass tube or a catheter with the opening on the end may be used to retrieve clot fragments. It seems reasonable to suppose that clots in the smaller vessels and portions of the main clot which are still present in the larger vessels might be "milked" proximally to the site of embolectomy by wrapping the leg firmly from the toes upward with a wide Para rubber bandage. Often, the small remaining portions of clot so impair the circulation as to prevent survival of the extremity after what appears to be a satisfactory embolectomy. This wrapping could be used, for the same reasons, in embolec-

tomy in the upper extremity and, because of the lesser muscle mass, might be more effective there.

The closure of the wound in the aorta is not difficult. The running mattress suture used here (Fig. 1) was entirely satisfactory. This is the same stitch as that used by Gross<sup>29</sup> in re-establishing the continuity of the aorta after excising the area of coarctation. One might believe that the success of such a closure would depend on the condition of the aortic wall and, in the presence of atheromatous changes, be inclined to reinforce the suture line with fibrin foam, oxycel etc., supported by an encircling cuff of chronic catgut as described by Jenkins.<sup>30</sup> Fascia as a reinforcing material might be considered, since an adequate supply would be available from either the anterior or posterior rectus sheath. However, in the cases reviewed by McClure and Harkins,<sup>2</sup> there was no instance of secondary hemorrhage as the cause of death.

As in other blood vessel surgery, the increasing number of successes is, to a large degree, due to the use of anticoagulants. Since the vessels of the lower extremities are the most likely places for the occurrence of postoperative thrombosis, heparin may be injected directly through the suture line in the aorta and be carried immediately into the vessels of the legs. It can also be given in the form of continuous intravenous drip, but the cardiac status of these patients warrants caution in determining the amount of fluid to be given this way and in its rate of administration. More recently, heparin has become available in a vehicle designed to permit slow absorption which, if effective, may simplify matters. As soon as the stomach is retentive, the administration of dicoumarol may be started. When the prothrombin activity has been sufficiently depressed, heparin may be discontinued.

Other postoperative measures of importance are attempts to dilate the vessels of the extremities either by interruption of the sympathetic fibers or by mechanical means, such as the use of intermittent venous occlusion or the alternating positive and negative pressure (Paevex). In the case reported herein, it seemed much more simple to administer a spinal anesthetic in order to provide vasodilatation bilaterally than to subject the patient to bilateral sympathetic blocks. One of the longer-acting agents (pontocaine) was used without untoward incident.

#### CONCLUSION

A case of successful removal of a saddle embolus of the aorta is reported. From a review of the available literature, it appears to be the 22nd case of this kind. Some general points in the etiology, diagnosis and management are discussed.

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# THE HISTOCHEMISTRY OF BURNED HUMAN SKIN\*†‡

With a Note on Base Exchange in Traumatized Tissue

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THE REQUIREMENTS OF THE BURNED PATIENT for sodium in therapy has been a subject of investigation and controversy in recent years. One aspect of this problem has turned on the question of whether or not there is a "selective" or "excessive" need for sodium in therapy. By this has been meant a need for sodium over and above that required to satisfy extra-cellular requirements; a need larger than that which could be satisfied by sodium in isotonic concentrations.

There are two mechanisms which might conceivably operate to produce such an excessive need for sodium. One would be the presence of sodium in increased concentration in the edema fluid of the burn, the other its presence in high concentration in the intracellular water. There is no evidence that the former exists; what knowledge we have of the burned capillary would indicate that burn edema fluid is in ionic equilibrium with other extracellular fluids. If the viable capillary allows Na and Cl to remain at essentially the same concentration on its two sides, there is little reason to postulate that the damaged capillary of the burn would be able to do the osmotic work required to bring about a concentration gradient.

Analyses of whole burned limbs<sup>1</sup> or observations on human patients given radiosodium<sup>2, 3</sup> do not yield data on selective sodium loss into the burn, since the increased tissue water in the area of the burn<sup>3</sup> would yield increases in apparent sodium volume and turnover even though concentration were not increased; the need thereby imposed could be met by the administration of isotonic sodium solutions.

In contrast to this extracellular isotonicity, the situation in the cell may be quite different. With sodium present in only small quantities normally, its ingress in increased amount—possibly in exchange for normal intracellular cations such as potassium or magnesium—could, theoretically at least, place a severe demand on body sodium resources, a demand which would not be met by isotonic sodium because, in exchanging for K, the sodium could move into the cell without a net water transfer<sup>4</sup>.

For this reason we have sought to investigate the histochemical changes in burned skin. Skin was chosen because of its obvious relation to the trauma,

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and its accessibility for study. Because of the normally small intracellular phase of skin it is a tissue unlikely to show quantitatively large cation transfer in response to trauma.

Electrolyte metabolism, as viewed in the burned patient as a total organism, is described in other investigations from this laboratory.<sup>3, 5</sup> Amongst other salient points the observation was made that the exudate loss of sodium often exceeded many times that of other routes of excretion.<sup>5</sup> Because of this permeation of sodium ion (and to a lesser degree chloride) through the burned tissue, the chemical composition of the burned tissue itself acquires additional importance.

#### METHODS

1. *Clinical.* Ten patients were selected, with both deep and superficial burns. Skin was removed for study under varying conditions. In deep full thickness burns generous portions of skin may be removed without anesthesia since the burn has destroyed the sensory nerve-endings; in some instances pentothal anesthesia was used, in others local anesthesia, care being taken to avoid introducing water directly into the portion to be studied. In two extensively burned patients who died within ten days of their injury the skin was removed immediately post mortem.

Unburned skin was also removed from burned patients for study, employing areas contralaterally symmetrical to the burn, so as to obtain skin of like thickness and histologic composition for comparison with burned tissue.

Skin was removed from healthy, unburned persons for control observations.

If radiosodium ( $\text{Na}^{24}$ ) studies were to be made, the  $\text{Na}^{24}$  was injected as isotonic saline (0.5 to 0.75 mc. in 10-30 cc.) from one to five hours prior to the biopsy.\* It was considered important to take the skin samples soon after radiosodium injection so as to bring out any differences in sodium exchange. If such a diffusible ion as Na is allowed to achieve physical (isotopic) equilibrium for 12 hours or more, acute differences in rate of uptake will not be demonstrated. In 12 to 24 hours equilibrium specific activity ratios ( $\text{Na}^{24}/\text{Na}^{23}$ ) will have been reached throughout most of the tissues, and minor permeability changes will not become apparent.<sup>6</sup>

2.  *$\text{Na}^{24}$  Analyses.* Immediately after removal from the patient the skin was mechanically freed of subcutaneous fat and weighed in portions 0.5-1.5 grams in size. Two, three or four such samples were prepared from each site, placed in a porcelain ashing capsule and ashed at a temperature safely below the volatilization point of sodium.†

\* Radioactive sodium ( $\text{Na}^{24}$ ) was prepared by the deuteron bombardment of metallic sodium at the Massachusetts Institute of Technology cyclotron. This sodium metal was then hydrated and neutralized, the resultant  $\text{Na}^{24}$  Cl being used for injection in patients after suitable sterilization by autoclaving.

† Control observations indicated the greater accuracy and reproducibility of this technic as compared with wet ashing methods, or nitric acid extract.

The radioactivity determinations were then carried out on this dry ash of skin, in the ashing capsule, by means of a Lauritsen quartz-fiber electroscope. Appropriate corrections for decay and self-absorption were made prior to calculation of the results.

3. *Water and Salt Analyses.* After radioactivity analysis the dry ash of skin was quantitatively transferred to glass and analyzed for  $\text{Na}^{23}$  by the method of Butler and Tuthill.<sup>7</sup> In a few cases chloride analyses were carried out, using the method of Wilson and Ball on a solution made of the dry ash.<sup>8</sup>

Duplicate tissue samples, after weighing, were taken to dryness at  $90^{\circ}\text{C}$  and then re-weighed to determine water content. These were then ashed and analyzed for sodium and chloride to corroborate the observations obtained from the samples used for  $\text{Na}^{24}$  determinations.

Much histochemical work, especially that based on analyses of muscle and viscera, is expressed on a fat-free basis. This is because of the fact that deposits of neutral fat add a variable weight increment which is relatively free of water-soluble constituents. The fat-free results therefore exhibit a lesser standard deviation from the mean and are more acceptable statistically. Skin, considered as dermis and epidermis only, contains relatively little neutral fat in fat cells; vigorous defatting procedures doubtless remove intracellular lipid-soluble material and squamous epithelium whose presence is necessary to the adequate description of the tissue. For these reasons and the fact that defatting skin (as opposed to other tissues) does not readily bring the tissue to constant weight, we have avoided defatting procedures in these studies. This results in a lower electrolyte content per unit skin by weight than one finds in "fat-free" skin.

4. *Calculations.*  $\text{Na}^{24}$ ,  $\text{Na}^{23}$ , chloride and water were calculated in relation to the weight of wet tissue (e.g. mE per Kg. wet tissue) and to the weight of tissue water (e.g. mE per Kg. tissue water). The calculations of extracellular space based on sodium and chloride concentrations were carried out by the formulas of Hastings and his group.<sup>9</sup> Other figures, derived from these fundamental calculations, will be described below.

## OBSERVATIONS

### 1. SODIUM CONTENT IN TERMS OF TISSUE WEIGHT

a. *Normal Skin of Unburned Patients.* In Table I is shown the sodium content of the normal skin of unburned patients. The mean sodium content in 21 such specimens was 74.0 mE per Kg. of wet tissue. Standard deviations\* represent about 10 per cent of the mean. These values run consistently lower than those reported by other workers who subjected the skin to a fat-freeing process. The work of Manery and Hastings based on fat-containing tissue in the rabbit is in the same order of magnitude as our results.<sup>12</sup>

b. *Unburned Skin of Burned Patients.* In Table II is shown the sodium content of the unburned skin of burned patients which appears to average about 10 mE/Kg. of wet tissue higher than the normal skin of unburned patients. This may be traceable to parenteral saline administered though it is

$$* \sigma = \sqrt{\frac{\sum d^2}{n}}$$

TABLE I.—*Sodium Content of Normal Skin.*  
mEq/Kg. Wet Tissue  
NORMAL SKIN OF UNBURNED PATIENTS

	No. of Samples	Mean	Standard Deviation
Pt. Mo. ....	10	78.86	± 4.51
Pt. McC. ....	7	66.8	± 6.96
Pt. Me. ....	1	65.2	
Pt. A. ....	3	78.0	± 7.15
<hr/>			
Total .....	21		
		74.0 (Average of all Samples)	
Eisele & Eichelberger (10).....	18	93.0	± 8.0 (Fat-free)
Eichelberger et al (dog) (11)...	..	96.5	± 4.2 ( " " )
Manery & Hastings (rabbit)(12)	..	79.6	

TABLE II.—*Sodium Content of Skin.*  
mEq/Kg. Wet Tissue  
UNBURNED SKIN OF BURNED PATIENTS

Case Number	No. of Samples	Mean	Standard Deviation
254 .....	3	72.0	± 3.87
229 .....	3	76.6	± 5.17
231 .....	2	79.1	± .01
217 .....	2	82.75	± 2.75
234 .....	3	88.3	± 2.5
210 .....	1	88.6	
240 .....	3	89.6	± 7.95
225 .....	6	96.0	± 5.56
<hr/>			
Total .....	23		
		85.5 (Average of all Samples)	

FULL THICKNESS BURNED SKIN				PARTIAL THICKNESS BURNED SKIN	
Case Number	No. of Samples	Mean	Standard Deviation	No. of Samples	Mean
217 .....	1	80.3			
234 .....	4	81.7	± 6.67		
240 .....	5	86.0	± 3.16	3	86.0
254 .....	4	92.5	± 2.28		
229 .....	3	95.8	± 5.56	4	82.2
210 .....	3	93.1	± 4.54		
231 .....	3	99.6	± 4.03	3	82.0
225 .....	4	117.2	± 2.95	2	103.0
<hr/>				<hr/>	
Total .....	27			12	
		94.5 (Average of all Samples)			89.0

of interest that some of the higher sodium contents were observed in patients who, because of the limited extent of their burns, received very little (or no) parenteral therapy.

c. *Burned Skin of Burned Patients.* In Table II are also shown values obtained from the burned skin of these same patients; an elevation of sodium content amounting to about 10 mE/Kg. of wet tissue as compared to the unburned skin is observed.

The burned skin from superficial (partial thickness) burns shows distinctly less increment.

The sodium content of full thickness burned skin shows more variation than the other data, for reasons to be described below.

*d. Sodium Ratios in Burned Skin.* Although the arithmetic mean of sodium content in burned skin is higher than that of unburned skin in the same patients, a more significant calculation is the ratio of sodium content in burned skin to that of contralateral unburned skin in the same patient.

Such findings are summarized in Table III. It will be seen that of these ten patients with deep burns, six showed a significant increase in sodium con-

TABLE III.—*Sodium Ratios.*

Case Number	Mean Sodium Content	Burned Skin Full Thickness	Burned Skin Partial Thickness
		Unburned Skin	Unburned Skin
234 .....	0.93		
240 .....	0.96		0.96
217 .....	0.97		
196a .....	1.09		
210 .....	1.11		
225 .....	1.20		1.07
229 .....	1.25		1.07
231 .....	1.26		
254 .....	1.28		
205 .....	1.30		1.04
Mean of Series.....	1.14		
Values between 0.90 and 1.10—No Significant Change			
Mean of Ratios Showing Significant Change	1.23		

TABLE IV.—*Water Content of Skin.*

Gm./Kg. Wet Tissue  
NORMALS

	Range	Mean	Standard Deviation
Eisele & Eichelberger (10).....	677-756	717.7	± 20.1
Eichelberger et al (dog) (11).....		708.3	± 20.1
Manery & Hastings (rabbit) (12)..	670-694	682.0	± 12.0
Massachusetts General Hospital....	578-678	630.0	± 32.6

## BURNED PATIENTS

Case Number	Full Thickness		Full Thickness Burn	Partial Thickness Burn
	Burn	Unburned	Unburned	Unburned
(A) Under 3 days after burn				
240 .....	675	680	0.99	1.01
254 .....	660	630	1.05	
225 .....	790	730	1.08	0.98
229 .....	758	659	1.15	1.12
217 .....	844	704	1.20	
196a .....	693	581	1.20	
Average of Ratios under 3 days.....			1.11	
(B) Over 3 days after burn				
210 .....	707	754	0.80	
205 .....	640	720	0.88	
234 .....	661	739	0.89	
231 .....	622	671	0.92	
Average of Ratios over 3 days.....			0.87	

tent. The whole series taken together showed a mean increase in sodium content of 14 per cent and those showing any increase at all showed an average increase of 23 per cent in the amount of sodium present. These same ratios for partial thickness burned skin are very close to unity, indicating no significant increase in the sodium content of superficially burned skin.

## 2. SODIUM CONTENT IN TERMS OF TISSUE WATER

If the burned tissue were simply edematous from collections of extracellular water, an increase in tissue water commensurate with the sodium increment should be observed; under such circumstances one would predict little or no alteration in sodium content expressed relative to tissue water rather than tissue weight.

Table IV and Table V contain data relative to this point. The water content of the skin observed in this series (Table IV) is somewhat lower than that found by Eisele and Eichelberger in normal skin which, as mentioned

TABLE V.—*Sodium Ratios in Tissue Water.*  
mEq/Kg. Tissue H<sub>2</sub>O

Case Number	Mean Sodium Content Tissue H <sub>2</sub> O	Burned Skin Full Thickness	Burned Skin Partial Thickness
		Unburned Skin	Unburned Skin
196 .....	0.78		
217 .....	0.80		
240 .....	0.98		0.95
225 .....	1.00*		0.86
234 .....	1.02		
229 .....	1.13*		0.95
210 .....	1.17*		
254 .....	1.22*		
231 .....	1.38*		1.02
205 .....	1.46*		
Mean of Series.....	1.09		
(mEq/Kg. Wet Tissue)....	1.14		
Mean of Increases.....	1.27		
(mEq/Kg. Wet Tissue)....	1.23		

Values between 0.90 and 1.10 — No Significant Change

\* Indicates patients showing significant increase in sodium content mEq/Kg. wet tissue

before, has been subjected to a fat-freeing process. It will be noted that in the fresh full thickness burns (less than three days duration) there is an increase in water content (as compared with the unburned tissue) amounting to 11 per cent. There are too few observations on partial thickness burns to be significant. In burns which occurred more than three days before the study was made, the ratios are consistently below 1.0 and show approximately a 13 per cent decrease in water content.

These figures indicate that freshly burned skin is in a state of water collection probably correlated with changes in capillary and cell permeability; this acute situation yields later to dehydration presumably due to loss from the sur-

TABLE VI.—*Radiosodium Uptake of Skin.*  
Specific Activity = Units of Radioactivity

Case Number	Specific Activity Full Thickness Burn	mEq. of Sodium Specific Activity		Full Thickness Burn	Partial Thickness Burn
		Unburned		Unburned	Unburned
(A) Under 3 days after burn					
196a .....	3.03	3.62		0.84	
229 .....	4.73	4.55		1.04	
217 .....	4.87	4.49		1.08	1.06
240 .....	9.52	8.25		1.14	1.03
225 .....	1.10	3.55		0.31	1.02
(B) Over 3 days after burn					
205 .....	4.47	8.23		0.54	
210 .....	4.45	7.22		0.61	
196b .....	5.14	5.57		0.92	

face by absorption into the dressing and evaporation into the air, resulting in a progressive desiccation of the full thickness burn.

When these data on water content are taken into consideration with the sodium content, as shown in Table V, we find that the sodium content (in terms of the weight of tissue water) is normal or increased in eight out of ten full thickness burns. Were the increase in sodium content to be due solely to changes in water content, we would find little or no increase in this figure. The data indicate that when the sodium concentration is expressed in terms of tissue water there is a greater spread than when sodium is referred to tissue weight, and the ratios (of burned to unburned skin) show more departure from unity. This suggests that in some of the cases, sodium may be moving independent of water transfer, whereas in others (cf. Table IV) the differential sodium accumulation is due largely to water loss.

In Table V, the entire series shows a nine per cent increase of sodium content when expressed in relation to the water content of the tissue. In the five cases showing increases, the average is a 27 per cent increase in sodium content as expressed relative to tissue water. It is of interest that these are the same five patients who showed an increase in sodium content when expressed in terms of wet tissue weight. Stated otherwise, when one measures the sodium content and expresses it solely as a function of the total tissue, one finds that there is an increase in sodium content. When this sodium concentration is expressed in terms of the amount of tissue water present, we find that the sodium increase is even more marked, pointing up the fact that the sodium is moving into the tissue in larger quantity than one would predict from the water content alone.

*In summary*, these data indicate that in the early phase after the burn, both sodium and water are moving into the skin. As the duration of the burn progresses past three days, and approaches a week, the tissue becomes increasingly dehydrated. The sodium that has entered the skin is probably not discharged as rapidly because evaporative water loss leaves the inorganic ions

behind. Therefore, as the skin becomes dehydrated, the sodium content relative to the total tissue water progressively increases.

### 3. SODIUM EXCHANGE

We now turn to a consideration of the exchange of sodium into the skin from the general circulation. This study was carried out by the use of radioactive sodium injected a few hours prior to the taking of the tissue samples, as described under "Methods".

Under these circumstances, sodium exchange may be studied by comparing the specific activity ratios, ( $\text{Na}^{24}/\text{Na}^{23}$ ), of burned to normal skin. If radio-sodium alone is determined the results are relatively meaningless as an increased content of  $\text{Na}^{24}$  may signify only the presence of more total  $\text{Na}^{23}$  (under equilibrium conditions), rather than any increased *rate* of uptake.

If the specific activity (amount of radioactive sodium per unit of total sodium) of the burned tissue is equal to that of the plasma or the unburned tissue, we may assume that equilibration has taken place and that exchange is complete at the time of sampling. We find in the fresh burns (Table VI), with one exception, that this exchange is complete; in one or two of the cases there is a tendency for a specific activity higher than unburned skin to be observed. The freshly burned tissue may take up sodium so rapidly that when it is sampled a few hours after the injection of the radiosodium, it still shows the high specific activities found in plasma a few minutes after injection, but which have been reduced in the plasma as the sodium equilibrated into other untraumatized tissues. This might be the explanation, for instance, of the specific activity ratio (burned/unburned skin) of 1.14 in patient 240.

Patient 225, (Table VI), showed, though only three days after the burn, practically no radiosodium uptake. This interesting and unusual finding was correlated with the fact that this was a dry flame burn resembling a "char" which doubtless lost its contact with the general circulation much earlier than the other full thickness burns.

From Table VI it is clear that those burns which are studied more than three days after burning tend to show a reduction in radiosodium uptake. This is evidence that the burn has lost contact with the general circulation and cannot enter into physical equilibrium with  $\text{Na}^{24}$ . Sodium ion is so readily diffusible that if there is any circulatory association whatever between the skin and the plasma, the tissue will rapidly take up the isotope and exchange it for its stable sodium. When this exchange does not take place, it is excellent evidence that the tissue is no longer in contact with the circulation.

### 4. HISTOCHEMICAL SODIUM SPACE

Table VII shows a series of calculations of the extracellular space of burned skin as based on the sodium and chloride content. This calculation is patterned after that developed by Hastings<sup>9</sup> and simply represents the amount of water in the tissue which contains sodium at the same concentration that it is found in plasma (when corrected for the Gibbs-Donnan effect and the variable water



TABLE VII.—“*Extracellular Space*” of Burned Skin.

As Per cent of Total Tissue Water

Concentration of (x) in wet tissue

100

$$E_x = \frac{\text{Concentration of (x) in extracellular water}}{\text{Concentration of (x) in extracellular water} + \text{Concentration of (x) in plasma adjusted for H}_2\text{O content of plasma and extracellular water; corrected for Gibbs-Donnan effect.}} \times \frac{\text{Total tissue water}}{\text{Total tissue water}}$$

		Concentration of (x) in extracellular water		Total tissue water	
		Concentration of (x) in extracellular water = (x) in plasma adjusted for H <sub>2</sub> O content of plasma and extracellular water; corrected for Gibbs-Donnan effect.			
Case		ENa Full Thickness	ENa Partial Thickness	ECl Full Thickness	ECl Partial Thickness
Number		ENa Unburned	ENa Unburned	ECl Unburned	ECl Unburned
A) Under 3 days after burn					
196a	.....	0.83			
254	.....	0.86		1.29	
240	.....	0.97	0.94	1.37	1.29
229	.....	1.09	0.96	1.08	0.87
225	.....	1.18	0.97	1.47	
		0.98 = Mean		1.30 = Mean	
B) Over 3 days after burn					
234	.....	1.10		0.81	
210	.....	1.18		1.10	
231	.....	1.39	1.02	1.29	1.20
205	.....	1.53			
		1.30 = Mean		1.06 = Mean	
Ena was found to be 100% of total tissue water in 6 out of 9 full thickness burns.					
Ecl was found to be 100% of total tissue water in 4 out of 6 full thickness burns.					

content of plasma and extracellular fluid). This space we called the “Ena.” A better term for it possibly is the “histochemical sodium space” emphasizing the fact that it is a tissue measurement of the sodium space made on exactly the same principle that the total radiosodium space is measured in the living patient by studying plasma concentration with relation to injected dose.

If the histochemical sodium space of a full thickness burn (expressed as per cent of tissue water) is the same as the histochemical sodium space of an unburned area of skin from the same patient, one may reasonably assume that the sodium in the burned tissue is still extracellular to the same extent that it is in the unburned tissue. If the histochemical sodium space of a full thickness burn were significantly larger than that of the unburned tissue, one would be forced to conclude either that the extracellular space in the burned tissue was much larger than that of the unburned tissue or that some of the sodium had moved into the cell. If, as a third possibility, the data indicated that the histochemical sodium space approximated 100 per cent of the measured tissue water, one would be forced to the conclusion that sodium had moved into the cells.

In five burns measured under three days after the burn (Table VII), the histochemical sodium space was almost exactly that of the unburned tissue with a mean value for this ratio of 0.98.

After three days, the histochemical sodium space has become expanded and represents approximately a 30 per cent increase over the Ena for normal tissue. In six out of nine of these patients the Ena was equal to 100 per cent of the total tissue water, evidence that sodium has moved into the cell.

This evidence concerning changes in the histochemical sodium space constitutes a chemical demonstration of the fact that full thickness burned tissue, after the third day, is dead tissue though still attached to the organism. Such skin is not exchanging ions with the body fluids of the patient; the normal property of the cell membrane which permits it to exclude sodium from the cellular fluids has been lost, with the result that sodium equilibrates evenly throughout the total tissue water.

5. PROTOCOLS OF TWO PATIENTS

Detailed consideration of two patients, the first a fresh deep burn in the fluid- and sodium-exchange phase, and the second a burn 48 hours after trauma,

TABLE VIII.—*Protocol of Patient 240*

A 5-year-old male child, flame burn of right lower leg from fire in clothing. Excised 4½° after burn, 1° 45' after Na<sup>24</sup> injection. Control skin taken from left thigh. No systemic fluid therapy. Burn "parclument-like," little edema, clinically clean. Bacteriology *Staph. albus* and *Alpha strep.* On penicillin.

	Normal Skin	Partial Thickness Burn	Full Thickness Burn	Plasma
H <sub>2</sub> O (gm/KG.)	680	682	675	935
Na <sup>24</sup> (u/Kg.)	737	735	817	1100
Na (mEq/Kg.)	89.6	86.0	86.0	132.6
Specific Activity	8.25	8.55	9.52	8.30
Cl (mEq/Kg.)	45.0	61.2	57.5	101.5
Ena (% Tot. H <sub>2</sub> O)	93	87	90	
Ecl (% Tot. H <sub>2</sub> O)	61	79	84	

in the "dry-dead" phase, may help in an understanding of the manner in which these data are derived.

In Table VIII (patient 240) are shown the data relative to a full thickness burn in a young child who received his radiosodium injection almost immediately upon arrival at the hospital and who was brought to the hospital very soon after his burn. It was possible to obtain a tissue sample only four and one-half hours after the burn which, in turn, was only one hour and 45 minutes after the injection of radiosodium. This permitted us to make an observation very early in the natural history of the histochemical changes of burned skin.

We find many features characteristic of the early burn. In the first place, the water content of the skin is unchanged. This is to be expected since there has been only a short time in which water content could be increased, there has been little opportunity for the development of edema. Radiosodium uptake, on the other hand, is increased over normal. This is a very delicate measurement of water and sodium exchange and it is apparent that at the time the skin was sampled, it was beginning to demonstrate increased rate of exchange with body fluids as compared with the exchange between normal skin and body fluids. The total sodium content is little changed, again because there has not been time for the accumulation of more total sodium.

The specific activity of the sodium present in this skin is increased about 10 per cent over that of plasma and the other tissues. The explanation of this,

as mentioned before, is to be found in the fact that the specific activity in this skin reflects the high specific activities of plasma an hour or so prior to the time the skin was sampled, at a time when skin was exchanging very rapidly with plasma. Chloride content is somewhat increased, but the Ena and Ecl are not 100 per cent of the total tissue water. They are instead indicative of an extracellular space about normal for skin.

The histochemical description of the skin of this burned child may be summarized by stating that it is a fresh burn which is still in contact with the cir-

TABLE IX.—*Protocol of Patient 225.*

A 54-year-old female; epileptic, burned on upper arm by flame during seizure; no systemic fluid therapy. Excised 48 hours later, 1° 20' after Na<sup>24</sup> injection. Skin "dead white," considerable edema, clinically clean. Bacteriology *Staph. aureus* and *Staph. albus*. No pre-op. penicillin. Control skin from opposite arm same level.

	Normal Skin	Partial Thickness		Full Thickness	Plasma
		Burn		Burn	
H <sub>2</sub> O (gm/Kg.)	730	810		790	935
Na <sup>24</sup> (u/Kg.)	335	373		121	481
Na (mEq/Kg.)	96	103		117	135
Specific Activity	3.55	3.64		1.10	3.57
Cl (mEq/Kg.)	64.0			91.7	108.0
Ena (% Tot. H <sub>2</sub> O)	91.3	88.6		100.8	-
Ecl (% Tot. H <sub>2</sub> O)	72.0			108.0	

ulation, it is exchanging sodium, and presumably chloride, more rapidly than is the normal skin in the same patient; there has not yet elapsed enough time since the burn for either water or total sodium to accumulate in the tissue and, lastly, that sodium and chloride are still confining themselves to the extracellular phase of the tissue and have not moved into the cell.

In contrast are the data on patient 225 (Table IX), the patient previously mentioned in whom a full thickness burn was associated with very little radiosodium uptake at 48 hours. It will be noted that this burn, excised 48 hours after the trauma, showed some increase in water content, a finding which probably was traceable to the fact that in the first 24 hours after the burn the skin was capable of accumulating measurable edema. The radiosodium uptake, on the other hand, is greatly diminished, as compared with normal skin or partial thickness burned skin taken from the same patient. The total sodium content in terms of mEq/Kg. of total tissue (wet weight) shows an increase over the normal skin. Again this is to be interpreted as evidence of the fact that sometime during the 48 hours which preceded radiosodium injection and excision, this skin had taken up both water and sodium in greater quantities than the normal skin in the same patient. The specific activity of the sodium in this burned skin (the ratio of Na<sup>24</sup> to Na<sup>23</sup>) is therefore less than that observed in normal skin from the same patient, by 30 per cent. It is also of interest that the specific activity of the normal skin, the partial thickness burned skin, and the plasma in this patient are all in equilibrium by the time of biopsy. Since these figures for specific activity (Na<sup>24</sup>/Na<sup>23</sup>) are derived from measures both

of radioactivity and total sodium in the tissue, they constitute a check on the accuracy of the methods. The specific activity ratios for these various normal tissues should come to unity with a readily diffusable ion one hour and twenty minutes after injection, as the observed values indicate.

The chloride content of this full thickness burned skin was increased. The

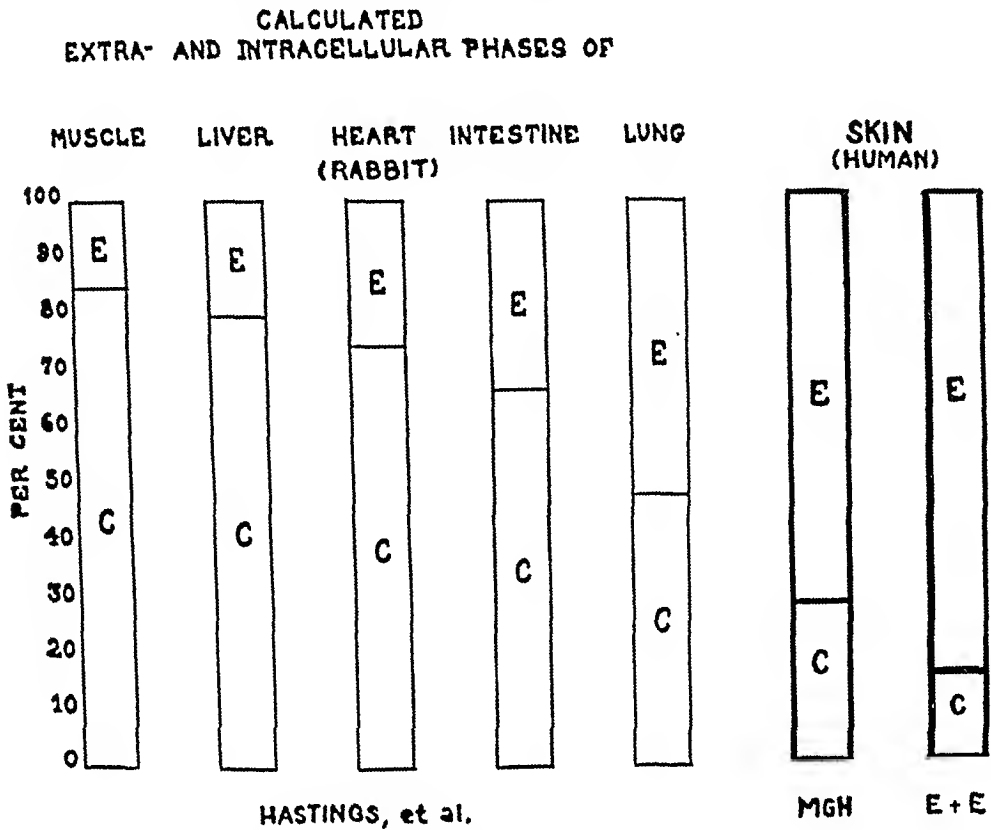


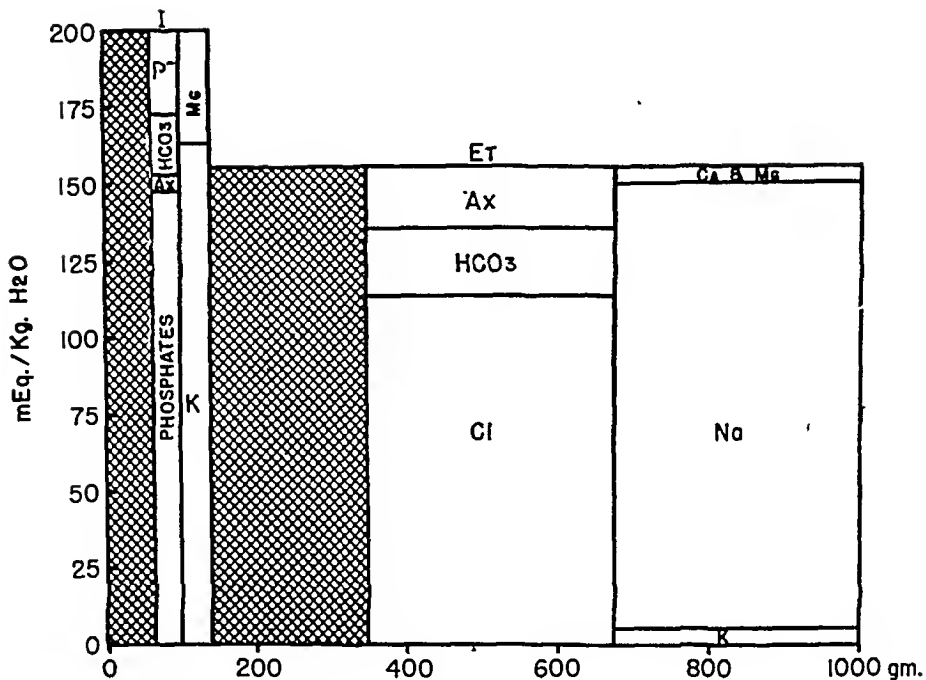
CHART I.—Diagrammatic representation of the relative intracellular and extracellular phases of various tissues. The extracellular phase is indicated by the letter "E," the intracellular phase by the letter "C." The rabbit data are those investigated by Hastings, et al., the human data are those reported herein ("MGH") and by Eisele and Eichelberger ("E&E").

Ena and Ecl both were increased and in the full thickness burned skin represented approximately 100 per cent of the total tissue water.

The data, then, allow us to characterize the burned skin from this patient as being skin which, sometime in its first 48 hours, took up water, sodium, and chloride but which, since that time, has lost its contact with the general circulation so that it is no longer exchanging ions with the plasma. The sodium and chloride in the skin have moved into the cell at essentially the same concentration at which they are found in the extracellular fluid.

#### DISCUSSION

An examination of histochemical concepts as applied to skin will aid us in an understanding of these data as well as the significance of possible sodium-potassium exchange in the cells of muscle after trauma. It must be emphasized that the great soft tissue mass of the body consists of striated muscle and that the skeletal muscles contain more protoplasmic protein than any other single tissue. When muscle, liver, kidney, lungs and heart are considered together,

NORMAL HUMAN SKIN  
(Adapted from Eisele & Eichelberger)

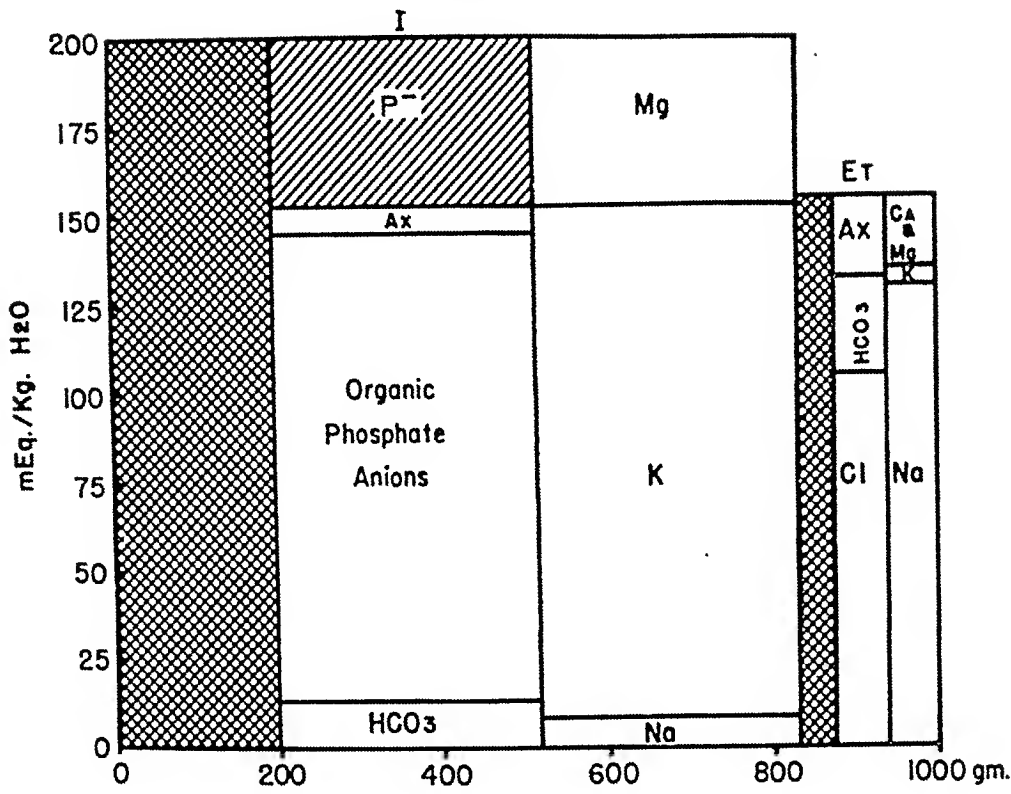
Fat Free				
Total H <sub>2</sub> O	= 718.0	Gm/Kg	wet	tissue
(H <sub>2</sub> O) E (NA)	= 638.0	" "	"	"
(H <sub>2</sub> O) c	= 80.0	" "	"	"
(H <sub>2</sub> O) E (Cl)	= 690.0	" "	"	"
Na	= 93.0	mEq/Kg	"	"
Cl	= 79.9	" "	"	"
K	= 16.47	" "	"	"
C.T.	= 216.0	Gm/Kg	"	"

CHART II.—Histochemical diagram of normal human skin. In this and the subsequent three charts, the horizontal coordinate is drawn in proportion to the weight of wet tissue, the vertical coordinate representing the concentration of solutes in tissue water. The symbol "Et" indicates extracellular tissue whereas the symbol "I" represents intracellular tissue. The relative concentration of anions and cations is shown in the two open columns within each tissue phase. The designation of the coordinates is such that the area within a subcompartment of the diagram is roughly proportional to the total weight of solutes present. A<sub>x</sub> indicates organic anions. The cross-hatched area represents non-ionized solids; in the case of extracellular tissue, this is largely collagen, elastin and other connective tissues and, in the intracellular phase, structure proteins.

Beneath the chart are shown some calculations of the quantities of water and solutes present. "(H<sub>2</sub>O)E(NA)" indicates the volume of extracellular water found by sodium analysis; "(H<sub>2</sub>O)E(Cl)" the same entity by chloride analysis. "(H<sub>2</sub>O)C" represents intracellular water (by difference). "C.T." signifies connective tissue. These data are derived from the work of Eisele and Eichelberger.

one has accounted for 95 per cent of the protein-containing cellular tissues of the body. No matter what their order of magnitude, it would be unlikely that histochemical changes in skin alone would be responsible for more than minor shifts of water and electrolyte, in terms of the total organism.

NORMAL SKELETAL MUSCLE  
(HASTINGS, et. al.)



Total H <sub>2</sub> O	= 752	Gm/Kg	wet	tissue
(H <sub>2</sub> O) <sub>E</sub>	= 122	" "	"	"
(H <sub>2</sub> O) <sub>C</sub>	= 630	" "	"	"
Na	= 19.0	mEq/Kg	"	"
Cl	= 12.8	" "	"	"
K	= 100.6	" "	"	"
C.T.	= 40.0	Gm/Kg	"	"

CHART III.—Histochemical diagram of normal skeletal muscle (Hastings). The method of depiction and the symbols used are the same as in Chart II. "P<sup>-</sup>" represents the equivalence of protein as anion.

An additional consideration has to do with the relative extracellular and intracellular compartments of skin as contrasted with other tissues of the body. In Chart I is shown a series of columns representing the division between extracellular and intracellular phases of tissues based on the determinations of Hastings,<sup>13</sup> and to this has been added the data on skin from our laboratory and from the work of Eisele and Eichelberger.<sup>10</sup> It will be seen from reference to this diagram that in skin the extracellular space dominates the tissue and that only a small compartment is within the cell. Histologic examination of dermis and epidermis, of course, corroborates this chemical determination in that the cellular layer is only 30 to 80 micra thick whereas the whole dermis may extend for four or five times that depth, the dermis being relatively cell-free. The calculations of extracellular space shown in Chart I are based on chloride and sodium analyses. It will be observed that muscle, liver and heart are all highly cellular tissues, quite removed from skin in their composition. There are few tissues of the body which contain less cellular material than skin and

these include such tissues as tendon and cartilage, tissues which are also relatively rich in sodium. Therefore, if one is considering exchange of ions between the cell and the extracellular compartment, it is quite apparent that muscle, liver or heart are much more capable of producing massive shifts of this variety than skin or other tissues low in cellular content.

In Chart II is shown a more detailed diagram of normal human skin based upon the data from Eisele and Eichelberger,<sup>10</sup> who made determinations of total connective tissue volume, which were not made in our series. It is again quite evident that over 80 per cent of the tissue is extracellular and that the sodium concentration is quite high in the tissue as a whole. Therefore, release

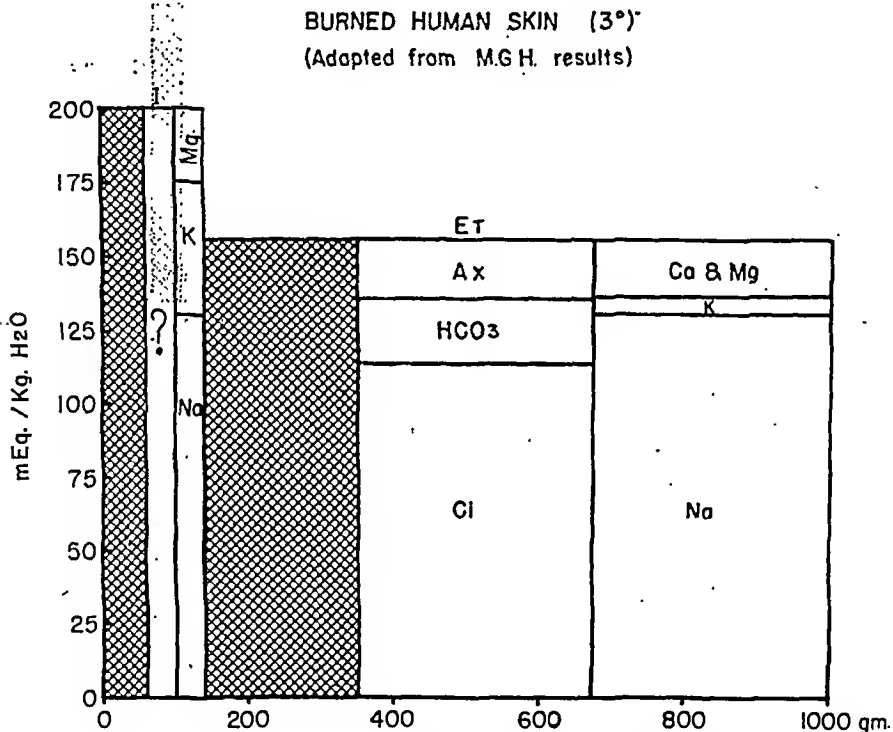


CHART IV.—Histochemical diagram of burned human skin. This chart is based on work reported herein; the chemical structure is still fragmentary. We have little evidence as to changes in intracellular anions. Sodium-potassium exchange is minimal despite the (relatively) great change in intracellular sodium.

of potassium from the cell or loss of sodium into the cell will inevitably be of minor importance relative to the organism as a whole.

In contrast to this is shown in Chart III an histochemical diagram of normal skeletal muscle. It is apparent that the tissue is over 80 per cent intracellular and that there is maximal opportunity for sodium-potassium exchange.

In Chart IV is shown a diagram of what might ensue in burned human skin were sodium and potassium to exchange in such a way that the intracellular sodium concentration were the same as that in the extracellular fluids. It is of interest that this theoretical calculation, (based on data from Eisele and Eichelberger,<sup>10</sup> and from Hastings<sup>13</sup>) indicates that skin would permit an

approximately 15 per cent increase in sodium content computed on the basis of total wet tissue. This is the same magnitude we have observed following burns, constituting another indirect evidence that the sodium shifts described in burned patients probably indicate the entrance of sodium into cells.

On the basis of the quantities shown in Chart IV, one may carry out approximate calculations indicating the deficit this "sodium loss into the cell" would create in the body as a whole if skin alone were involved. In a 70-kg man of average height and assuming a 50 per cent burn, approximately four and one-half kilograms of skin would be burned as a maximum. This would impose a sodium deficit on the patient of only 35 mEq, which could be sup-

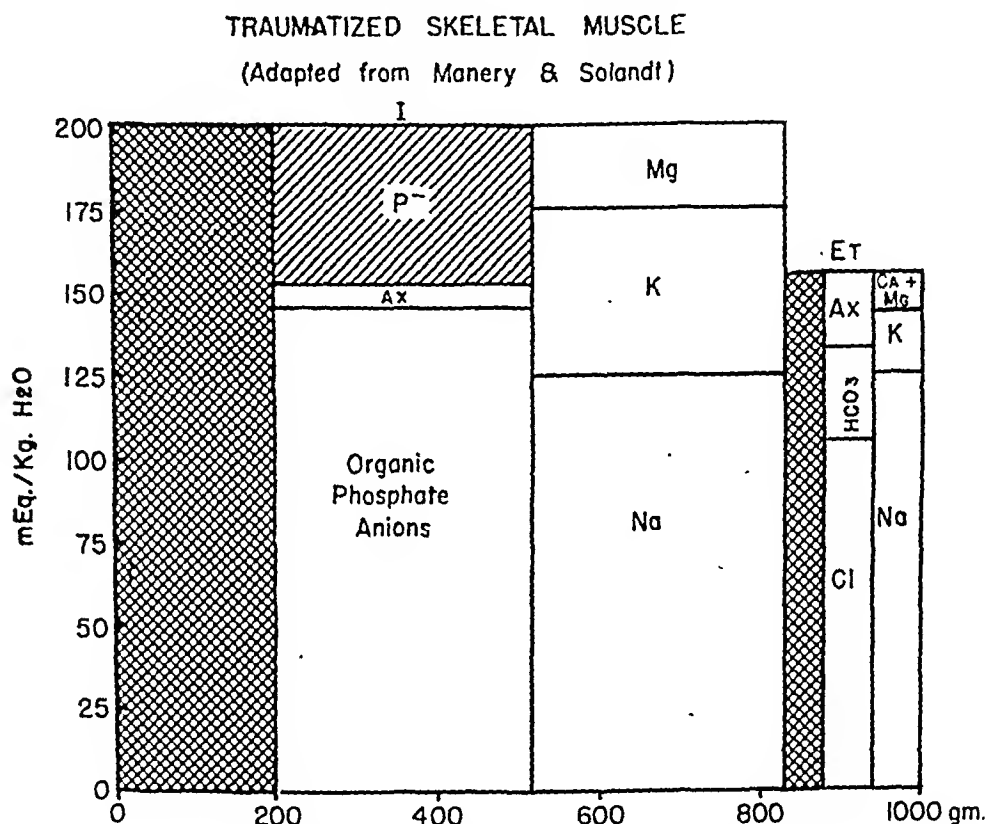


CHART V.—Histochemical diagram of traumatized skeletal muscle. This is based on the work of Manery and Solandt; the mass of sodium and potassium exchanged is very large, due to the relatively large size of the intracellular compartment.

plied by only 450 cc. of normal sodium solution, an amount which is approximately one-twentieth of that usually required in the first 24 hours of a burned patient's treatment.

The potassium release from this skin would theoretically total 35 mEq, and with an extracellular volume of 20 liters, this would increase the potassium concentration only 1.9 mEq/L, assuming that there is no excretion.\*

In contrast to this situation, in Chart V are shown the chemical events which would ensue were 10 Kg. of muscle mass to be so traumatized that

\*The excretion is, in fact, increased during such situations and potassium concentration in the plasma has not been observed as significantly increased in our experience with burned patients.



sodium-potassium exchange could occur. Such an event might consist of trauma involving ischemia to the muscle, or some such injury as a crush. One may calculate the potential sodium-potassium exchange involved in such muscle trauma; the changes would present the body with a sodium deficit of about 640 mEq which would require almost five liters of normal saline to satisfy, and the potassium release would be so massive as to increase the potassium concentration to toxic levels (15 mEq/L or higher), providing renal function did not take care of this excess.

#### SUMMARY AND CONCLUSIONS

1. The histochemical changes in burned human skin are described.
2. The established histochemistry of skin and muscle are contrasted with respect to their potential for cation transfer.
3. From these data, observed and calculated, we may conclude that, following burns, the entrance of sodium into skin cells is evidence of cell death; it is an alteration in tissue chemistry of great local significance. From the viewpoint of the total organism, however, such alterations impose little sodium deficit and no discernible potassium excess.
4. Were similar changes to occur in skeletal muscle, massive electrolyte transfer would seriously alter the chemical composition of both intracellular and extracellular fluid, and endanger survival.

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# POLYPOID ADENOMATOSIS OF THE ENTIRE GASTRO-INTESTINAL TRACT\*

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THE CHILD WHOSE HISTORY is the basis of this report presented a remarkably interesting and confusing clinical picture which was finally elucidated only by autopsy.

**Case 1.**—R. T., A-44010. The patient was a white male infant, first admitted to the Harriet Lane Home in October 1945 at the age of 10 months. He had been born by breech delivery after a difficult labor and had been cyanotic for the first four days of life. From birth he had suffered from diarrhea with numerous large, foul stools—up to twelve daily. Despite a good appetite and ample food intake he failed to gain weight, and it was observed that food passed unchanged in the feces. He had coughed almost from birth and at the age of nine months had been treated elsewhere for "bronchopneumonia." In the succeeding month he had lost five pounds in weight and had become weak and pale.

On physical examination the child presented a picture of advanced malnutrition and cachexia. He was pale, weak and lethargic, and coughed frequently. He weighed only 7500 Gm., had only 2 teeth, could not walk, crawl, or sit up, and was scarcely able to hold up his head. There were generalized inspiratory rales and the liver and spleen were enlarged. It was thought, with the diarrhea, malnutrition, and chronic pulmonary disease, that the child had cystic fibrosis of the pancreas, but the duodenal enzyme studies failed to support the diagnosis. When the child was placed on a metabolism bed to permit studies of stool fat, he had a rectal prolapse (Fig. 1), exposing many polypoid tumors on the rectal mucosa, some almost 2 cm. in diameter.

An ordinary gastro-intestinal series and barium enema failed to show any lesion. There was "chronic non-tuberculous infiltration" of the lungs on roentgenographic examination and bronchoscopy revealed diffuse bronchial inflammation with purulent secretions. A second barium enema finally showed numerous polyps (Fig. 2) in the colon. Rectal prolapse became a chronic recurrent condition until the polyps were removed with the cautery loop. Roentgenograms were made by introduction of barium through a Miller-Abbott tube which had been passed into the small intestine. No polyps were seen.

Considerably improved by numerous blood transfusions, the child was discharged. It was thought that he had polypoid adenomatosis of the colon and it was felt that colectomy would be required for relief. He was to be followed in the out-patient department pending the result of experimental investigation of the feasibility of total colectomy and anal ileostomy with preservation of the sphincter. Sigmoidoscopy of the mother and of the putative father showed no polyps in the rectum of either and neither had any suggestive symptoms.

In February 1946, three weeks after discharge, he was readmitted because of a mild balanitis. Rectal prolapses of major proportions recurred frequently and diarrhea had continued. His condition aside from the balanitis did not change during the two weeks of this admission.

In May 1946, when he was 18 months old, he was admitted to the Harriet Lane Home for the third and last time. The rectum had prolapsed on four more occasions and he continued to have three to seven loose, bloody stools a day. Edema of the legs had increased progressively for three weeks. He now weighed only 8600 Gm. and appeared cachectic with progeric facies. There was generalized edema and the clubbing of the fingers and toes, which had developed during the first admission, was more prominent than before.

\* Submitted for publication, July, 1948.

He still had a constant cough and the fine rales were still present throughout both lungs. The hemoglobin was 10.5 Gm. The total serum protein was 3.33 Gm. per cent, albumin 2.34 Gm. per cent, globulin 0.99 Gm. per cent, with an A/G ratio of 2.36. Numerous other blood chemical determinations gave results within the normal range. Again the pancreatic enzyme studies gave results in the normal range. The lungs were clear on roentgenographic examination. He was transfused repeatedly. On May 29, 1946, he began to have obvious abdominal pain, and after about 18 hours a mass was felt in the left



FIG. 1.—R. T., age 11 months.—Rectal prolapse showing numerous adenomata of considerable size.

lower abdomen; he became distended and vomited, and the diagnosis of intussusception was made.

At operation (Dr. W. E. Grose) there was found a bluish discolored intussusception a foot long, involving the ileum and reaching almost to the ileocecal valve. The intussusception was rapidly resected and an end-to-end anastomosis performed. Many polyps were felt in the small bowel well above the intussusception. The resected bowel was gangrenous and showed numerous polypoid adenomata, many of them large and pedunculated. The child tolerated the procedure surprisingly well, but had progressive difficulty with respiration and died 24 hours after operation.

Autopsy 19978, May 31, 1946. The entire intestinal tract from the cardia of the stomach to the anus was involved in a remarkable process. Every segment was affected and no areas were "skipped." The mucosa was covered with innumerable polypoid tumors, the character and distribution of which varied from segment to segment. The stomach (Fig. 3) was the seat of a great number of polyps, most of them large, measuring one to several centimeters in diameter, usually sessile but occasionally pedunculated. There were numerous smaller pedunculated duodenal polyps. (Fig. 4.) The entire jejunum and

ileum were spotted with polyps, as shown in the photographs. (Fig. 5.) The anastomosis had been performed a few centimeters above the ileocecal valve and appeared to leak after the adherent bowel had been separated at autopsy. It was felt that in life an adjacent loop had sealed the leak. The colon (Fig. 5) was carpeted with polyps, large and small,



FIG. 2.—R. T., age 11 mos. Barium enema.—Numerous round radiolucent areas are seen in both right and left colon. As seen in Fig. 5, the bowel was literally carpeted with adenomata. Only a few tumors are revealed by the barium enema.

sessile and pedunculated, for its entire length. The terminal 10 cm. of the rectum, in which the polyps had been fulgurated months before in an attempt to prevent repeated rectal prolapse, now showed only small polyps. The pancreas was normal. There was emphysema and patchy atelectasis of the lungs. The child had the hippocratic osteoarthropathy of fingers and toes which had been recognized in life. No other disease was

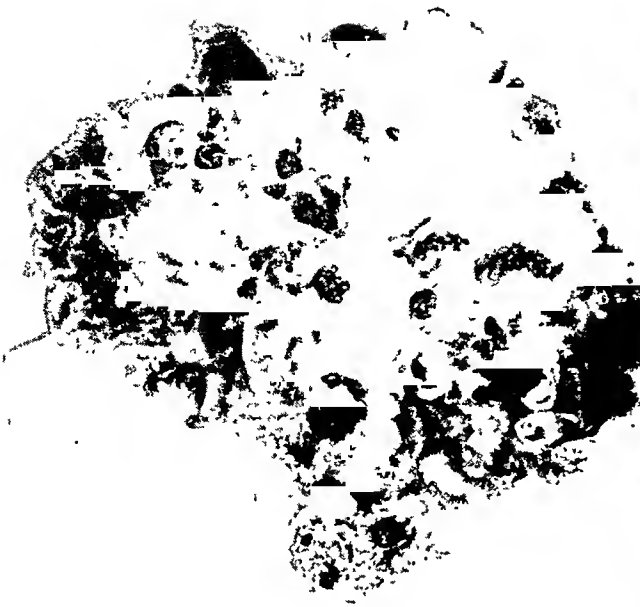


FIG. 3.



FIG. 4.

FIG. 3.—R. T., age 18 mos. Autopsy specimen of stomach.—There are numerous polypoid tumors, most of them large (up to 3 cms. diameter) and many of them ulcerated.

FIG. 4.—R. T., age 18 mos. Autopsy specimen.—Duodenum with attached segment of liver. There are many adenomata, mostly pedunculated, and much smaller than those in the stomach.



FIG. 5.—R. T., age 18 mos. Autopsy specimen.—Every segment of the small bowel is spotted by great numbers of tumors. The large bowel is even more heavily seeded and the tumors tend to be larger. In the last few inches of rectum and anal canal the adenomata, though numerous, are very small due to the previous electro-surgical section. The end-to-end anastomosis is just proximal to the cecum.

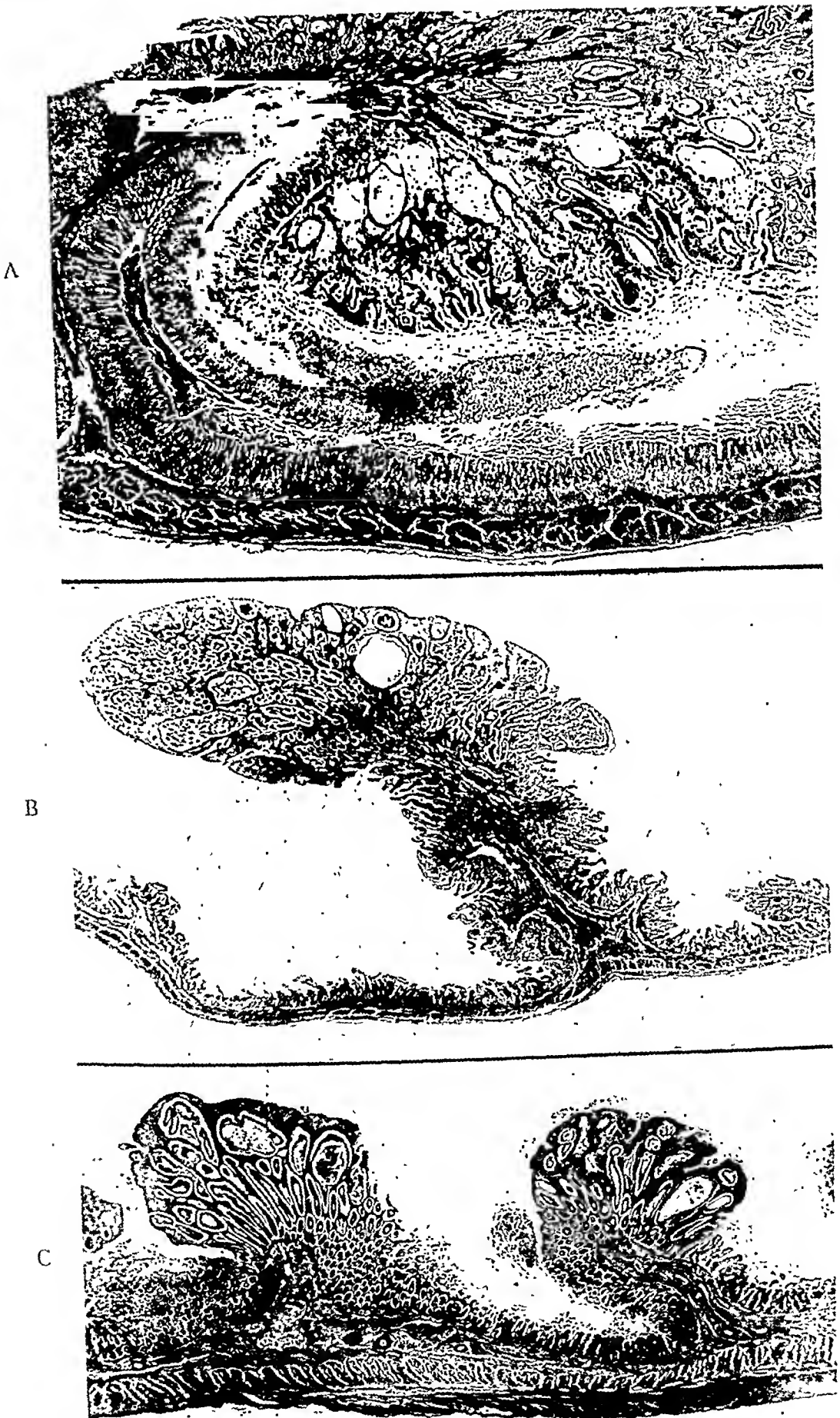


FIG. 6.—Photomicrographs of tumors of R. T.—A. Section of gastric polyp  $\times 10$ . The tumor is a true polypoid adenoma, being composed entirely of a mass of glands. B. Jejunal tumor  $\times 10$ . This tumor is more pedunculated and the fibrous stroma has been pulled out into the base. C. Section of the colon  $\times 10$  showing that the polyps are almost contiguous.

found, but the diffuse gastro-intestinal adenomatosis. Sections of the polyps presented the usual picture of true adenomata, as illustrated in the photomicrographs. (Fig. 6.)

A second patient was seen recently on the private service of Dr. I. R. Trimble. At operation she was shown to have polyps of the stomach and of several segments of the small bowel. Rectal polyps were visible through the sigmoidoscope. The precise degree of involvement in her case can not as yet be stated with certainty.

Case 2.—J. E., 439670. A white girl, aged 16 years, was first seen in this hospital in 1937 at the age of six. At that time she was being studied for severe chronic secondary anemia with bloody stools and repeated attacks of abdominal pain with audible peristaltic

rushes. While on the ward and before a diagnosis had been made, an obvious intussusception developed. Abdominal exploration by Dr. I. R. Trimble revealed two separate intussusceptions of the small intestine, one associated with a single polyp and the other with two polyps. These intussusceptions were rather far apart, one being in the mid-ileum, the other in the terminal ileum. The intussusceptions were reduced and the polyps excised. Convalescence was uneventful.

The child had been noticed almost from birth to have peculiar brown pigmented spots on the vermillion portion of her lips and on the adjacent mucous membrane (Fig. 7). The significance of these was first appreciated on the present admission because of the previous clinical observations of Dr. Victor McKusick in similar cases.<sup>17</sup>



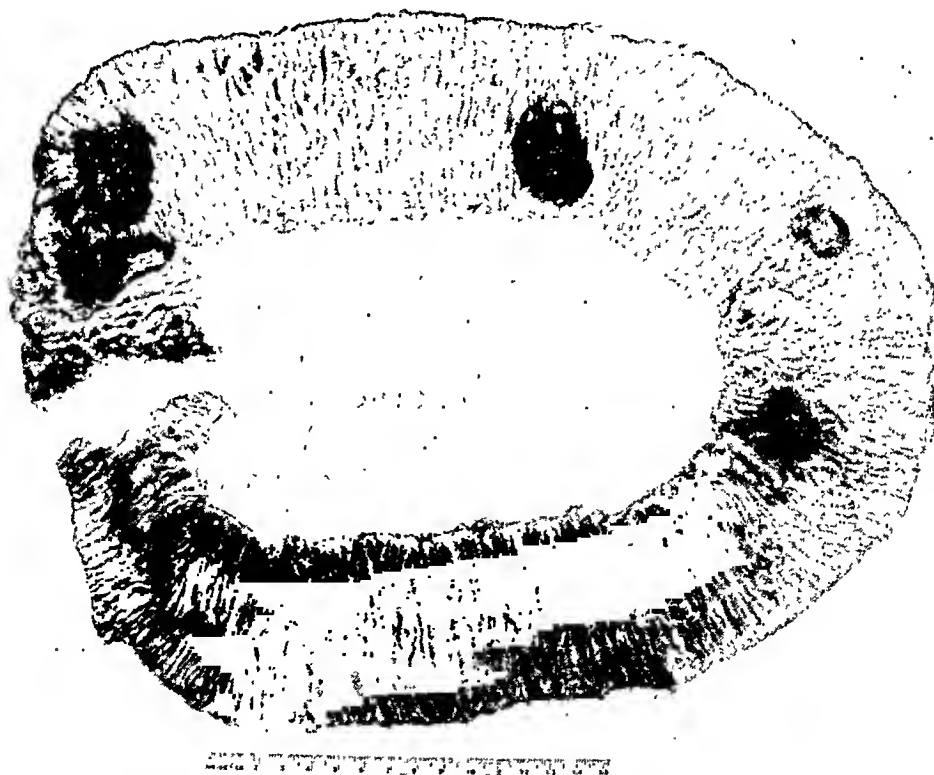
FIG. 7.—J. E., age 16 years. The pigmented patches on upper and lower lip are plainly seen. Others are within the mouth.

After her operation she remained well until 2 or 3 years before the present admission, when repeated attacks of abdominal pain began, accompanied by a chronic secondary anemia. She had been taking iron constantly by mouth so that it was not possible to draw any conclusions from the color of her stools. There had never been any massive hemorrhage and she had never had diarrhea, tending rather to be constipated. The attacks of pain might last as long as 24 to 36 hours with cramps one or two minutes apart. No attack had been as severe as the one for which operation had been performed. However, during one particularly severe attack 2 years before her present admission she was operated upon in her home community and obstructing bands of adhesions were divided. She was occasionally nauseated with her attacks, but vomiting was rare. Sigmoidoscopic examination and repeated roentgen studies of the entire gastro-intestinal tract were negative.

On physical examination she was seen to be a bright, alert girl of 16, thin and very pale. There were numerous peculiar irregularly-shaped flecks of brown pigment on the lips and oral mucosa, varying in size from 1 to 2 or 3 mm. in diameter. (Fig. 7.) There was no definite clubbing of the fingers or toes, although the distal phalanges of the fingers were suggestively spatulate. The abdomen was scaphoid. There was a well healed lower midline scar. No masses were felt and there was no tenderness. Digital rectal examination was negative. Laboratory tests: hemoglobin 8.2 Gm., red blood cells 3.39 million.

## POLYPOID ADENOMATOSIS

A



B

FIG. 8.—J. E., age 16 years.—A Photomicrograph  $\times 10$  of one of two polypoid tumors removed from stomach by gastrotomy. B. Segment of jejunum resected at second operation and containing 6 large polypoid adenomata. This patient had rectal tumors seen through the sigmoidoscope.



total serum proteins, 5.9 Gm. per cent, stools—positive guaiac test for occult blood, urine negative.

On sigmoidoscopy two small rectal polyps were seen within 10 cm. of the anus. Repeated roentgenographic studies of colon, stomach, and small intestine, the latter being made with barium introduced through an indwelling tube, all failed to show polyps.

After repeated transfusions of whole blood, on October 31, 1947 operation was performed by Dr. Trimble. Two separate large polyps 1.5 cm. in diameter were palpable in the stomach and were removed by gastrotomy. (Fig. 8a.) A segment of jejunum about 100 cm. long was found to contain eight large pedunculated polyps, the largest being 2.5 cm. in diameter. This segment of bowel was resected (Fig. 8b) and an end-to-end anastomosis performed. Recovery from operation was smooth, and the child was discharged on November 25, 1947, much improved.

#### POLYPOID ADENOMATOSIS OF THE COLON

The literature on polypoid adenomatosis is confused by the inclusion under this heading of many patients with only a few, six or eight, polyps of the colon. Such patients have multiple polyps, indeed, but not polypoid adenomatosis. Their disease is not familial, the prognosis is more favorable, and the required treatment less radical since removal of the individual tumors is adequate treatment. In true polypoid adenomatosis the entire colon, or a large segment of it, is the seat of innumerable polyps. The polyps vary in size from those just barely visible to the naked eye to those several centimeters in diameter, either sessile or pedunculated. Under the heading of "polyposis coli" in the literature are found many reports of the condition more properly described as familial polypoid adenomatosis of the colon. There have by now been several hundred such cases reported. Since Cripps' original observation<sup>2</sup> of the familial incidence of the disease, many instances have been reported of patients in whose family trees there was a high incidence of this condition.<sup>3, 4, 5</sup> Bensaude, Hillemand, and Augier<sup>6</sup> have reported several patients in whom polypoid adenomatosis of the colon was accompanied by clubbing of the fingers and sexual infantilism.

The feature of prime importance in colonic adenomatosis is the inevitable development of cancer in one or several such adenomata. It is repeatedly stated<sup>7, 8</sup> that all patients with polypoid adenomatosis will ultimately have cancer of the rectum, if they survive long enough, and the incidence of cancer in various series, as of the time of the given report, has been as high as 43 per cent.<sup>9</sup>

The diagnosis is based on the history, on digital and visual examination of the rectum, upon a properly performed double contrast barium enema, and lastly by operation. It has been our experience that the barium enema may demonstrate only a few of the larger polyps, as can be seen by comparing the picture of the specimen of R. T. (Fig. 5) with the roentgenogram (Fig. 2) of the same patient. It is noteworthy, furthermore, that polyps may be excessively difficult to palpate at laparotomy, as exemplified by a 25-year-old man who was seen recently. His mother had polypoid adenomatosis with three separate carcinomas of the left colon, and his three sisters all had bloody diarrhea and typical sigmoidoscopic findings. Multiple minute polyps and one larger polyp

## POLYPOID ADENOMATOSIS

A



B

FIG. 9.—B. McG., age 26.—Specimen removed at first operation. A. Entire specimen. Numerous larger adenomata are seen. The smaller ones, as in the cecum, are almost invisible. B. Close-up of cecum (left) and rectum (right). Note the great number of very small mucosal tumors. It was impossible to feel these at the time of operation.

about 0.5 cm. in diameter were found on sigmoidoscopy of the patient but barium enemata were equivocal. At laparotomy careful palpation revealed only one polyp in the entire colon, and that one on the left side, probably the one seen through the sigmoidoscope. Nevertheless, it was felt that he must have polypoid adenomatosis, and a total colectomy was begun, in this first stage resecting the colon from the ileocecal valve to the rectum. The specimen (Fig. 9) showed the bowel carpeted with polyps for the length of the specimen.

The treatment advocated is indicated above—total colectomy with a permanent ileostomy, preferably anal as recently reported.<sup>10</sup> Several authors have reported successes with subtotal colectomy and repeated fulguration of the rectum. This is a dangerous half measure. The mucosa of the remaining segment retains its genetic predisposition to polyp formation with the ultimate risk of cancer. There are a number of reports of cancer developing in the preserved rectal segment and we have seen this occur once<sup>10</sup> after such a procedure.

#### POLYPOID ADENOMATOSIS OF THE SMALL INTESTINE

Adenomatosis of the small intestine is different in many respects from familial adenomatosis of the colon. It has only occasionally appeared to be familial. Reisinger<sup>11</sup> operated upon a father and a daughter for repeated intussusceptions due to multiple jejunal polyps. Malignant degeneration has occurred<sup>12, 13, 14</sup> but is uncommon. Adenomatosis of the small intestine is apt to manifest itself by repeated bouts of abdominal discomfort, sometimes vague, sometimes exceedingly acute. These attacks apparently indicate intestinal obstruction due either to the polyps themselves or to associated intussusceptions. The most characteristic feature in the histories of reported cases is the frequency of repeated operations for intussusception. Gatersleben<sup>13</sup> cites four patients with multiple polyps of the small intestine who had together been operated upon for intussusception on ten different occasions.

Diagnosis has been very difficult and is rarely made before operation, which is generally undertaken for an attack of acute intestinal obstruction due to intussusception. Raiford<sup>15</sup> stated that 23 per cent of patients with benign tumors of the small intestine had intussusception. In several instances we have attempted roentgenography unsuccessfully by a double contrast method, introducing the barium and air into the bowel through an indwelling tube passed to the small intestine. Jeghers<sup>16</sup> and McKusick<sup>17</sup> have individually rediscovered and remarked upon Hutchinson's observation of peculiar pigmentation of the buccal mucosa in some patients who subsequently proved to have polyps of the small or large intestine, as in the second patient described in the present report.

The treatment of polypoid adenomatosis of the small bowel depends on the extent of the disease. The jejunum is apparently the segment of the small intestine most commonly affected by large numbers of polyps (Beales,<sup>18</sup> Struthers,<sup>12</sup> Shaw,<sup>19</sup> Atakam,<sup>20</sup> Björkroth<sup>21</sup>). It is much more rare to find the entire small intestine involved in polypoid disease (Reisinger,<sup>11</sup> Manfredi<sup>22</sup>). If all

the polyps occur in one segment of small intestine it is probably worth-while to resect that segment. Elective resection is hardly warranted if the polyps are scattered through the entire length of the small bowel or if there are polyps in the colon (Niemack<sup>23</sup>) or in the stomach (Wechselman<sup>24</sup>). In such instances one adopts a more or less passive attitude. Operation is performed only when demanded by the occurrence of an intussusception, and then the segment involved should be resected rather than reduced and left behind.

#### POLYPOID ADENOMATOSIS OF THE STOMACH

Polyps of the stomach, even when multiple and covering most of the stomach, may be peculiarly silent. Pearl and Brunn<sup>25</sup> reported 125 collected cases, in which they found no evidence of familial incidence. Of the 37 patients most recently reported, cancer had developed in 19 by the time of the report. Pearl mentions the well-known difficulty of demonstrating gastric polyps roentgenographically. It has frequently been reported that stomachs which are the seat of numerous polyps have appeared normal in the gastro-intestinal series. The roentgenograms of R. T. failed to demonstrate the innumerable polyps (Fig. 3) in the stomach. Polyps may cause vague malaise, indigestion, melena, or hematemesis, or a large polyp occluding the pylorus may at times produce intermittent obstructive symptoms.

Radical gastrectomy is the treatment of choice for gastric adenomatosis (Pearl and Brunn,<sup>25</sup> Kaarstad<sup>26</sup>) not associated with adenomatosis of other portions of the intestinal tract. The likelihood of malignant degeneration is at least as high as it is in polypoid adenomatosis of the colon. In the absence of any obvious genetic factor it is probably not necessary to perform total gastrectomy, provided no polyps are seen by direct inspection of the mucosa of any portion of the stomach which can be left behind. In the stomach, even more than in the small or large intestine, palpation through the thick bowel wall cannot be relied upon to reveal polyps, and if they are suspected and not felt, gastrotomy must be resorted to before it is safe to state that the stomach is free of polyps. The incidence of gastric polyposis associated with colonic or rectal polyposis is too high to be accidental (Gejrot,<sup>27</sup> Wechselman,<sup>24</sup> Port,<sup>28</sup> Schöttler<sup>29</sup>). The occurrence of these potentially malignant lesions at both ends of the gastro-intestinal tract poses a difficult surgical problem.

#### POLYPOID ADENOMATOSIS OF THE ENTIRE GASTRO-INTESTINAL TRACT

The patient presented first in this report aroused our interest because of the simultaneous occurrence of polypoid adenomatosis in several segments of the intestinal tract. The number of instances reported is not large and only two substantiated similar instances have been found of adenomata carpeting the intestinal tract from the cardia to the anus. There were ten additional reported cases in which each segment of the intestinal tract, beginning with the stomach, had at least a few polyps.

Glass<sup>30</sup> reported two instances of diffuse polypoid adenomatosis of the gastro-intestinal tract. The most striking case was a female patient who was followed for 19 years. From the age of 12 she had had postprandial cramps

and vomiting and had been thought to have a duodenal ulcer. In 1918, when she was 20, Dr. Charles Mayo operated upon her for a three-day attack of intestinal obstruction and removed four duodenal polyps. In 1919 she was operated upon for an intussusception of the ileum and three feet of bowel were resected, containing many polyps "as large as a lime." She remained well until 1928 when another intussusception was reduced and four polyps were removed. In 1929 she was operated upon for rectal bleeding and one large sigmoid polyp, three rectal polyps, and one cecal polyp were removed. In 1930 Dr. Fred Rankin performed a left colectomy. In 1935 she was acutely ill at the Memorial Hospital in New York, under the care of Dr. George T. Pack. The stomach was found to be filled with polypoid masses and resection was considered inadvisable. Autopsy disclosed generalized gastro-intestinal polyposis.

The other patient reported by Glass was a male of 27 with symptoms of hematemesis and melena who was found on roentgenography to have polyposis of the entire gastro-intestinal tract. Further details are not given.

The best substantiated report of polypoid adenomatosis involving all of the gastro-intestinal tract was that of Brachetto-Brian and Lascano<sup>31</sup> who reported the case of a 53-year-old female with vomiting, tenesmus, and bloody diarrhea of one week's duration and a palpable mass on rectal examination. She died after resection of the rectum for carcinoma. At autopsy the stomach was found to be covered with large polyps, sessile and pedunculated, and the entire small intestine was covered with polyps, with multiple but fewer discrete larger polyps in the colon. The sigmoid tumor measured 5 by 6 cm. and was frankly malignant.

Petrow's<sup>32</sup> is one of the earliest reports. His patient, a 26-year-old female, was operated upon for a gangrenous ileocecal intussusception of 15 days' duration and died. There were multiple gastric polyps, pedunculated duodenal polyps, and multiple polyps of the remainder of the gastro-intestinal tract. The title of the report indicates malignant degeneration of one of the polyps. The original article has not been available for the present report.

Shaw,<sup>19</sup> in reporting five cases of polyposis of the small intestine states that in the Rhode Island Hospital there has been one autopsy of a case of polyposis of the entire gastro-intestinal tract.

Hauser<sup>33</sup> in 1895 reported the case of a man of 33 who died after resection of the rectum for cancer. He had huge polypoid rectal masses and a left colon filled with polyps. There were somewhat fewer polyps in the transverse and ascending colon. In the ileum and jejunum there were small sessile polyps and in the duodenum, great numbers of polyps. In the stomach were many small polyps.

Schilling,<sup>34</sup> among others, mentions the dissertation of Schöttler<sup>29</sup> which we have been unable to obtain. This is said to be a report in detail of two instances of adenomata involving the entire gastro-intestinal tract.

Wechselman<sup>24</sup> reported an instance of what he impressively termed "Polyposis adenomatosa universali intestini totius," an autopsy finding in a 62-year-

old man dying of pneumonia. There was a large polyp of the stomach, another of the duodenum, and three in the jejunum, and the entire colon was thickly seeded with polyps of all sizes. Wechselman mentions, without citing it, a case previously reported which he considers questionable, and gives the list of Versé's<sup>35</sup> collected cases. We have reviewed the originals of the accounts quoted by Versé and the acceptable cases are included in the present report.

Funkenstein's<sup>36</sup> patient was a 24-year-old female who had had abdominal pain, vomiting, and bloody diarrhea for two years. She was edematous and had clubbed fingers. The red blood cell count was three million. She succumbed with a severe diarrhea. At autopsy she was found to have three pyloric polyps, six duodenal polyps, and innumerable large and small colonic polyps.

Gütig and Herzog<sup>37</sup> report a 16-year-old female who had been operated upon for intussusception four years before. An extensive segment of polyp-bearing small intestine had been resected. Roentgen studies showed polyps in stomach, small intestine and colon. Another intussusception occurred and at operation polyps were felt in stomach and small intestine. Death ensued. At autopsy two polyps were found in the stomach, fairly numerous large polyps in the small bowel, and two polyps in the colon.

Avidon<sup>38</sup> reported an 11-year-old boy with a two months' history of vomiting. Operation disclosed a polyp of the pyloric antrum which was resected. The child continued to vomit and operation disclosed a large jejunal polyp with retrograde intussusception, gangrene, and obstruction. He died after the resection, and at autopsy five gastric polyps, six small intestinal polyps, and one polyp in the colon were found.

#### POLYPOID ADENOMATOSIS OF SMALL AND LARGE INTESTINE

There are a number of reports of adenomatosis with this distribution of lesions. The histories combine the pain and repeated intussusception of adenomatosis of the small intestine with the diarrhea and malignant degeneration of adenomatosis of the large intestine. The condition usually is not familial. In the absence of a familial history, in patients with adenomatosis of the colon, the small intestine must be explored before a colectomy is performed. This is a therapeutically hopeless condition if the adenomata are widespread and numerous. However, resection may be feasible if the tumors involve only a few bowel segments of limited extent or if only a few large polyps are scattered about.

A Cabot<sup>14</sup> case report described a 36-year-old male ill with vague symptoms in the course of which he had one brief period of diarrhea and finally jaundice. Autopsy disclosed a diffuse polyposis of the intestinal tract from one millimeter beyond the pylorus to one centimeter above the internal sphincter ani. The intestine was carpeted with polyps and one, at the ampulla of Vater, had become malignant.

Mandillon and Georget<sup>39</sup> report a 21-year-old male whose brother died at the age of seven of intestinal obstruction and whose sister had been operated upon for intussusception due to a polyp. This patient had numerous polypoid rectal adenomata, and at laparotomy a segment of ileum two meters in length was found to bear innumerable polyps. Instead of resecting this segment the

authors removed the six largest polyps. The patient underwent four subsequent operations for intussusception of the small intestine.

In 1931 Tonnesen<sup>40</sup>, reviewing the occurrence of intestinal polyps, stated that 73 per cent of reported cases and 82.5 per cent of his own cases of polyposis were of the rectum. For the stomach the figures were 7 and 12.5 per cent. In addition to Wechselman's cases already cited, he added one case of polyps in stomach, ileum, and colon; one in stomach, cecum, colon, and rectum; one in stomach and rectum. Tonnesen also cites the report of Aisman<sup>41</sup> from Russia. Aisman had two cases of polyps in ileum, colon, and rectum; one in stomach, jejunum, and ileum; one in stomach, duodenum, and colon; one in the entire intestinal tract except the jejunum.

Niemack's patient<sup>23</sup>, a girl of twelve years, died after three years of abdominal pain and intractable bloody diarrhea. She was found to have diffuse intestinal polyposis with heaviest involvement in ileum and colon.

Versé<sup>35</sup> collected two instances of diffuse involvement of the ileum and two others of diffuse involvement of ileum and colon.

Schöttler<sup>29</sup> in addition to two cases involving the entire intestinal tract, is said to have reported one patient with polyposis of large and small intestine, two patients with polyps of the ileum, one with polyps of rectum and stomach, and one with polyps of stomach and small intestine.

Sklifasowski,<sup>42</sup> whose Russian report is abstracted by Port and by Mandillon and Georget, described an instance of polyposis of the entire small intestine, found at operation in 1881 in a man of 51 known to have multiple rectal polyps.

Gottesman and Perla's patient<sup>43</sup> died at the age of 44 after years of bloody diarrhea and had multiple polyps of large and small intestine.

The patient of Devic and Bussy<sup>44</sup> was a female of 36 years. She died of acute mesenteric thrombosis and was found to have multiple polyps from the proximal duodenum through the jejunum, which was practically obstructed, throughout the ileum and into the cecum and colon, which were covered with polyps down to the sigmoid where polyps became fewer.

In Farmer's<sup>45</sup> case there was extensive polypoid adenomatosis of the small and large intestine. There was no autopsy, and the state of the stomach is unknown except that the patient had had her first hospital admission for "gastric ulcer." She had intermittent abdominal pain and occasional vomiting but no diarrhea or melena. At her first operation two large jejunal polyps were removed. At her second operation two years later a large segment of polyp-bearing small intestine was resected. Three years after that she had a sudden collapse with massive rectal bleeding, and barium enema revealed diffuse polyposis of the rectum and colon.

Nato Campanella's case<sup>46</sup> is perhaps the most extreme instance of involvement of both large and small intestine in polypoid adenomatosis. An infant of five months, who had had diarrhea and occasional vomiting, developed intussusception of the jejunum and died of a massive hemorrhage. At autopsy the intussuscepted bowel appeared still viable. There was a diffuse involvement with polyps from 10 cm. beyond the pylorus to the anus.

The presence of adenomata in the stomach may complicate treatment in patients with polyps of the small intestine. Wechselman collected two such instances.

#### SUMMARY

Any segment of the gastro-intestinal tract and any combination of segments may be the seat of numerous adenomatous polyps.

In the colon polypoid adenomatosis is a well recognized disease entity with familial incidence. Prolonged bloody diarrhea leads to anemia and cachexia. Total colectomy is required to obviate the inevitable carcinomatous transformation of one or several of the adenomata.

In the stomach, adenomatosis causes vague symptoms. Resection of the tumor-bearing segment relieves the symptoms and prevents malignant degeneration of the polyps.

Adenomatosis of the small intestine is only occasionally familial. It is manifested by melena, anemia, and repeated intussusception. When the polyps are limited to segments of moderate length, resection is feasible.

Two cases are reported in each of which all segments of the gastro-intestinal tract were involved in polypoid adenomatosis. There are a number of descriptions of adenomatosis occurring in several segments of the bowel simultaneously and a few instances, such as those reported here, in which adenomatosis involved all segments of the gastro-intestinal tract.

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## TUMOR OF THE SMALL INTESTINE\*†

### Miller-Abbott Tube Determines Site of Massive Hemorrhage

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RECENTLY PUBLISHED LITERATURE contains many reports of cases of massive hemorrhage from the gastrointestinal tract. An article by Baker and Halley includes an excellent review of the recent outstanding literature dealing with benign tumors of the small intestine and covers the subject well. Such a review here would be repetition.

Numerically, tumors of the small intestine are about equally divided between the benign and the malignant type. By far the commonest malignant tumor is the adenocarcinoma. In an article read recently before the Georgia Medical Society, Good stated that 26, or approximately 42 per cent, of a series of 61 tumors of the small intestine seen at the Mayo Clinic were adenocarcinomas, and 10, or about 16 per cent, were leiomyomas. While leiomyomas constitute only a small percentage of the tumors of the small intestine, there is frequently doubt as to whether they should be considered benign or malignant. It is certain that many of them eventually become malignant.

Tumors of the small bowel, whether benign or malignant, occur most frequently in the proximal portion. Symptoms are variable and by no means dependable, but the commonest one is bleeding, which is estimated to occur in about 35 per cent of cases.

The case reported here is one of massive intestinal hemorrhage from a tumor of the small bowel. Histologically, this tumor appeared to be benign, but it was classified by the Army Institute of Pathology as a leiomyosarcoma. This case illustrates many of the common symptoms of this condition as well as some of the diagnostic difficulties encountered.

#### REPORT OF CASE

M. E. G., Sr., a white man aged 63, was admitted to the Fort McPherson Station Hospital on March 5, 1947 in a state bordering on shock. Approximately two hours previously, he had fainted without warning in a downtown hotel lobby and when taken to his room, had had two copious stools of dark red blood. When he was admitted to the emergency room of the hospital, he complained of cramps in the lower portion of the abdomen and extreme weakness. He estimated that he had passed approximately 1 quart of dark blood per rectum before admission.

Approximately 10 years prior to this time, the patient had experienced a similar episode, following which a complete roentgen examination of the gastro-intestinal tract together with appropriate hematologic studies had been made, with negative results except for a slight filling defect of the duodenum. Exploratory laparotomy at that time had revealed an entirely normal stomach and duodenum. No reason could be found for the slight roentgen evidence of irregularity in the duodenum. The small intestine had

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appeared entirely normal. With the exception of vague indigestion and irregular bowel habits, the patient had lived normally until approximately four months prior to admission, at which time he had had another massive intestinal hemorrhage. Roentgen studies had demonstrated the presence of a small diaphragmatic hernia. It was suspected that the hemorrhage had resulted either from an ulcer in the lower portion of the esophagus or the upper part of the stomach, or from esophageal varices. The bleeding had stopped completely, and no further treatment was sought.

Physical examination revealed a well developed and nourished white man, lying quietly in bed in no acute pain. He was extremely pale, almost matching in color the sheets on the bed. The pulse was weak but regular, with a rate of 100; the temperature was 97.6 F. Aside from slight generalized abdominal tenderness, the physical examination gave essentially negative results. The red blood cell count was 4.1 million with hemoglobin 70 per cent (12 Gm. Sahli); the hematocrit reading was 26 cc. per hundred cubic centimeters of blood; the total protein content was 5.75 Gm., the albumin 3.10 Gm. and the globulin 2.65 Gm. per hundred cubic centimeters of blood; and the albumin-globulin ratio was 1.17 to 1.

The patient was given plasma and heavily sedated. The following morning, he was given 500 cc. of whole blood slowly, with no further evidence of hemorrhage. At this point, with 2,000 cc. of matched blood available, a Miller-Abbott tube was passed for diagnostic purposes. The bleeding point was established approximately 5 feet beyond the stomach. He was then given a liquid diet high in protein and carbohydrates, and was transfused at intervals. On March 9, the hematocrit reading was 32 cc., and the red blood cell count was 3.5 million. It was decided that this would be an ideal time for exploration as his general condition seemed excellent.

At operation, the incision was made in the right upper quadrant of the abdomen through the scar resulting from the previous laparotomy, and the peritoneum was opened with difficulty because of underlying omental adhesions. These adhesions were dissected free, and the peritoneal cavity was entered. Careful examination of the liver revealed no nodules and no evidence of metastasis. The gallbladder emptied normally. Because of rather dense adhesions, the stomach and duodenum were not examined. Starting at the ligament of Treitz, the small intestine was carefully examined throughout its entire length. Approximately 3 feet from the duodenum, a small intussusception was encountered, which reduced spontaneously as it was examined. No cause could be found for the intussusception, and at the close of the operation its exact location could not be determined by examining the bowel. Approximately 4 feet from the duodenum, a large intussusception was demonstrated. The cause for this was a small tumor (Fig. 1) on the antimesenteric side of the intestine. There was great increase in vascularity in the mesentery at this level. One or two small buckshot-sized nodes were palpable near the intestine in the mesentery, but no distant nodes could be palpated. The bowel was resected approximately 4 inches on either side of the tumor, and an end to end anastomosis was performed. Routine closure of the abdominal wall was carried out, and the patient's immediate postoperative condition was satisfactory.

On the day following the operation, the total protein content of the blood was 5.68 Gm., albumin 3.54 Gm. and globulin 2.14 Gm.; the albumin-globulin ratio was 1.65 to 1. The general condition of the patient seemed excellent. On the second postoperative day, the blood values were total protein content 5.11 Gm., albumin 3.75 Gm. and globulin 1.36 Gm.; the albumin-globulin ratio was 2.7 to 1. At this time the red blood cell count was 3.55 million, the hemoglobin 58 per cent (10 Gm. Sahli), and the hematocrit reading 31 cc.

From this point the patient made an uneventful recovery. Sutures were removed on the eighth postoperative day, at which time the wound was well healed. The red blood cell count was at that time 3.6 million with hemoglobin 73.5 per cent (12.5 Gm. Sahli). He was allowed out of bed on the fourth postoperative day and by the eleventh

day was able to be up most of the time. He was discharged from the hospital on this date.

The pathologic report from the Army Institute of Pathology follows: "The tumor nodule, which is well circumscribed, lies in the wall of the jejunum. It interrupts the muscular layer laterally, closely underlies and elevates the epithelium on the mucosal aspect, and extends to the serosa by way of a nipple-like extension. Its structure is compact, consisting of fusiform-shaped cells arranged in interlacing strands and bundles.



FIG. 1.—This photograph shows the tumor protruding into the jejunum.

The nuclei, depending upon the plane of section, are round to rod-shaped. They are rather pale with finely granular diffusely scattered chromatin and a single moderately conspicuous nucleolus. There is mild variation in the size and shape and staining qualities of the nuclei. Mitotic figures are not seen. The appearance and staining properties of the cells indicate an origin from smooth muscle. Vascularity is moderate; the vessels are thin-walled, consisting in many instances of only an endothelial layer which appears to be directly opposed to the tumor cells. In recognition of the treacherous course of smooth



FIG. 2.—Photomicrograph showing a cross section of the tumor (magnified 6 times)

muscle tumors of the intestine, the lesion in this case is being coded as a leiomyosarcoma despite its relatively innocent histologic appearance" (see Fig. 2)

#### DISCUSSION

This case is being reported largely for a discussion of the diagnostic procedure used. It is recognized that this procedure has great potential dangers, and, except for the fact that the patient had had two previous severe hemorrhages followed by every conventional diagnostic test including exploratory laparotomy, it would have been considered too dangerous to use. With 2,000 cc. of blood matched with that of the patient ready for immediate use, a Miller-Abbott tube was passed into the stomach and the contents aspirated and tested for blood. It was then passed under fluoroscopic vision through the duodenum with samples being taken in the second and third portions of the duodenum. The tube was then advanced approximately 6 inches at one hour intervals, and a sample of the intestinal content was withdrawn each time. When the tube had been passed approximately 5 feet beyond the end of the stomach, dark blood was withdrawn for the first time. A roentgenogram was made to establish the location of the tube, and the tube was thereafter immediately withdrawn.

The Miller-Abbott tube gave an accurate picture of the location of the source of this patient's bleeding. It made possible exploratory laparotomy with a fairly definite aim in view. Exploration revealed the tumor at approximately four feet from the ligament of Treitz, or about where it was expected the lesion would be found. The tumor was evident and would have been easily discovered upon exploration, but since one exploration almost ten years previously had

failed to demonstrate the site of hemorrhage, it was feared that the same difficulty would be encountered again. It is by no means certain that the first hemorrhage which the patient experienced was due to the same lesion as were the last two hemorrhages.

This procedure is not recommended as a routine diagnostic aid. It is thought, however, that in rare instances when plenty of blood is available and immediate surgery can be instituted, it may be a helpful diagnostic aid.

#### SUMMARY

Tumors of the small intestine are discussed briefly.

A case is reported in which the pathologic diagnosis was leiomyosarcoma of the jejunum.

In this case massive hemorrhage was localized by the passage of a Miller-Abbott tube.

Despite its potential dangers, this procedure may occasionally be a valuable diagnostic aid in selected cases.

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# RECURRENT PRIMARY THROMBOCYTOPENIC PURPURA WITH ACCESSORY SPLEENS\*

## Review of the Literature

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WERLHOF in 1731, laid the foundation for our present concept of the disease which bears his name, and which also is described as "purpura hemorrhagica." However, in the eighteenth century, the spleen was unsuspected of being associated with thrombocytopenic purpura. In 1916, Kaznelson,<sup>2</sup> while still a medical student, favored the theory that hypersplenism was responsible for lowered platelet counts. This resulted from an observation which he made, namely, that in three of four cases of thrombocytopenic purpura, he found a splenomegaly. At his insistence, he persuaded Shloffer of Prague to do a splenectomy on a patient suffering from chronic thrombocytopenic purpura; this resulted in a dramatic response. In 1921, Finkelstein<sup>3</sup> was probably the first to call attention to the fact that accessory spleens might be responsible for the recurrence of symptoms in postsplenectomy essential thrombocytopenia, and in 1928, Morrison, Lederer and Fradkin<sup>4</sup> reported two cases of accessory spleens associated with this condition. The role played by unremoved accessory spleens following splenectomy for primary thrombocytopenic purpura has been stressed by Curtis and White,<sup>5</sup> Vaughan,<sup>6, 7</sup> Robertson,<sup>8</sup> Maingot,<sup>9</sup> Curtis and Movitz,<sup>10, 11</sup> and Watson and Moir.<sup>12</sup>

Despite the fact that such significance has been placed upon unnoticed splenicules, few cases are reported. Watson and Moir<sup>12</sup> record recurrent purpuric manifestations in a case following therapeutic splenectomy in which a 2.5 cm. diameter accessory spleen was found at necropsy. A similar case appears in the article of Curtis and Movitz.<sup>11</sup> These latter two authors have established the importance of accessory spleens in showing that in 174 consecutive cases of splenectomy, and in four abdominal explorations, they found 131 accessory spleens in 56 patients, an incidence of 32 per cent. The number of accessory spleens varied from one to ten.

Recurrence of primary thrombocytopenic purpura is reported by Giffin and Holloway<sup>13</sup> as 14 per cent, and Vaughan<sup>7</sup> as 17 per cent. What percentage of such recurrences results from accessory spleens is unreported, but it is suggested by Watson and Moir,<sup>12</sup> that the incidence of the recurrences closely resembles that of accessory splenic tissue reported by pathologists. Adami and Nichols<sup>14</sup> report 11 per cent in their necropsies; the incidence at Cook County Hospital is 10 per cent; Emmet and Dreyfuss<sup>15</sup> record 10 per cent and Morrison et al<sup>4</sup> report 35 per cent after adoption of a systematic search. Increased incidence of accessory tissue in primary splenic disease is reported

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by Maingot<sup>10</sup> (44.4 per cent), Curtis and White<sup>5</sup> (20 per cent), McLaughlin<sup>17</sup> (24 per cent), and Curtis and Movitz<sup>11</sup> (31.4 per cent).

Splenic "seeding" should be considered during the removal of the spleen for such diseases as primary thrombocytopenic purpura and congenital hemolytic icterus, especially when recurrence follows. Such accidental "seeding" is suggested by Curtis and Movitz.<sup>11</sup> McLaughlin<sup>17</sup> has reported a case of recurrent congenital hemolytic icterus in a splenectomized patient, in whom generalized so-called abdominal "hemolymph" glands were found enlarged at necropsy; it was thought that these were splenic type tissue. The successful transplantation of such tissue into subcutaneous and muscle layers by Putschar<sup>18</sup> and Perla,<sup>19</sup> and the observation by several writers<sup>20-29</sup> of multiple intra-abdominal splenic tissue islets following trauma to the spleen, suggests the possibility of relapse by gradual assumption of splenic functions by these new growths. No instance, however, is reported in which such nodules following surgery for rupture of a normal spleen have resulted in primary splenic disease.

Buchbinder and Lipkoff<sup>29</sup> have termed the "seeding" of multiple splenic transplants through the abdominal cavity following splenic trauma as "splenosis," and this condition technically should be differentiated from the presence of true accessory splenic tissue. It is probable that the 400 accessory spleens reported in 1896 by Albrecht<sup>20</sup> and the case he cites by Orth were of this category.

While "splenosis" as described above follows no general plan, there are certain generalities to be noted concerning the locations of true accessory spleens. Since minuteness in no way eliminates the tissue as a cause of future recurrence, a definite plan of search should be followed to remove these offenders. Schilling<sup>21</sup> lists the possible sites in this order of frequency: (1) splenic hilus, (2) gastrosplenic omentum, (3) great omentum, (4) edge of the omentum, (5) splenocolic ligament, (6) pleurocolic ligament, (7) peritoneum along the splenic vessels, and (8) pancreas. Curtis and Movitz<sup>10, 11</sup> list: (1) the hilus of the spleen, (2) the pedicle of the spleen, (3) the retroperitoneal region around the tail of the pancreas, (4) the omentum, especially at the greater curvature of the stomach, (5) splenocolic ligament, (6) the mesentery of both small and large bowel, and (7) the left adnexa in females. The latter authors surprisingly found that 85 per cent of patients with accessory spleens had them in a single location, and that in no instance were more than two locations found. In addition, where such was the case, one of the double sites was always hilar. Even in unusual cases, such as Olken's,<sup>30</sup> a second hilar accessory was found in addition to a left scrotal splenicule.

#### EMBRYOLOGY

Splenic anlagen first appear in the 8 mm. embryo,<sup>31</sup> on the left side of the dorsal mesogastrium, as an accumulation of mesenchymal cells, just beneath the surface (peritoneal) epithelium. These appear as several small "hillocks" whose subsequent fusion forms a single organ. The survival of one of these may result in a lobulated or accessory spleen. Whether this abnormality occurs



cephalad, caudad or ventrad to the main mass, and whether it arises early or late in embryonic life determines roughly the location of the splenicule.

Curtis and Movitz<sup>11</sup> have given an excellent review of the underlying embryologic principles and consider five phases of splenic development sufficient to explain all accessory spleens. They are the following: (1) the manner of formation of the major spleen with its notches and lobulations by fusion of the separated splenic masses; (2) the formation of accessories by failure of fusion of the separate anlagen; (3) the formation and development of the subjacent dorsal mesogastrium into the various ligaments and bursae carrying along the accessory spleens to their various distant future locations; (4) the development of the splenic artery and its branches providing a similar blood supply to the splenic lobules and the accessories, with the accessory merely representing a greater degree of "fusion failure" than the lobule; (5) the embryonic contiguity of splenic anlagen to the genital ridge (on medial side of the mesonephros) permitting an accessory spleen to become attached to the left gonad.

Although the spleen is part of the blood system of the body, Keith<sup>32</sup> considers its development with organs of digestion since he thinks it must originally have been part of the alimentary system. Its origin is connected with the stomach, and its blood like the alimentary tract enters the portal circulation. The spleen grows from the left surface of the dorsal mesogastrium above the cardiac end of the stomach. It appears at the beginning of the sixth week as a localized growth of mesoderm. In the third month, the dorsal splenic surface is nodular and deeply fissured, and at the middle of fetal life these fissures begin to disappear but only persist on the anterior (gastric) border.

#### PATHOLOGIC PHYSIOLOGY

C. A. Doan<sup>33</sup> has done much to clarify the modern concept of the physiology of the spleen from an organ of complete mystery to one of understandable functions. Although much information concerning the spleen is controversial, certain facts seem fairly well established. This organ seems to have the following three structures: (1) a reticulo-endothelial system; (2) a vascular system; (3) a lymphoid system. The smooth muscle in the capsule and trabeculae together with the vascular system serve as the structural basis for the blood reservoir function of the spleen. The reticulo-endothelial system is made up of "specific endothelia," and a reticulum endowed with special phagocytic powers.

The normal spleen is concerned with blood cell destruction, formation and sequestration. A delicate splenic equilibrium results which may be upset by either congenital or acquired causes, resulting in diminution or accentuation of these physiologic processes. By means of supravital studies on splenic parenchyma, it has been shown that the spleen may become hyperactive with a resulting increase in number and phagocytic power of the macrophage. This has been referred to as hypersplenism. If this overactivity focuses on the red blood cells, congenital hemolytic icterus results; if it focuses on the thrombo-

cytes, then essential thrombocytopenic purpura results; and if the granulocytes are affected by the destructive process, a condition designated as primary splenic neutropenia results.<sup>34</sup>

When such a spleen becomes hyperactive, the bone marrow tries to compensate for the destruction and loss of blood elements. However, the spleen usually gains the upper hand and the involved blood cells are kept at a pathologic low level. Should an overactive spleen fail to discriminate between the elements which pass through it, red cells, granulocytes and platelets all may be destroyed simultaneously, resulting in a condition called pansplenic hematocytopenia. In such patients, a marked compensatory hyperplasia of the bone marrow results.

#### CASE REPORT

J. H. (46-58183), a 22-year-old white married female, entered Cook County Hospital November 25, 1946, complaining of an aching pain in the "right side" for 4 days, which was accompanied by vomiting and constipation.

*History.* History revealed that the patient, in her youth, suffered severe epistaxis once every two months, and also had marked gingival bleeding. After menarche at 14 years, she experienced prolonged menstrual periods which always lasted from one to two weeks with onset at 30-day intervals. These were described as not excessive but merely prolonged.

In April 1943, a slight injury resulted in a large bruise over the anterior forearm and arm. She consulted her family doctor who immediately had her hospitalized for observation. She recalls the diagnosis as "purpura" and states that she received "shots" in the deltoid area; however, she stopped these voluntarily.

In August 1943, following severe vaginal bleeding, the patient consulted a gynecologist and was immediately hospitalized. She received 6 transfusions, and a splenectomy was performed. She remained in the hospital for about 2 weeks, her vaginal bleeding stopped, and the small red spots which were present on her legs gradually disappeared. Postoperative platelet counts unfortunately were not done.

Thirty days after the preceding hemorrhage, another severe vaginal hemorrhage occurred and following its cessation, in approximately 10 days, the patient received radium therapy via a vaginal pack. Although her ecchymoses and gingival bleeding persisted and the small red spots continued to appear, she had no vaginal bleeding until May 1945, when she had a scant three-day flow. These facts should have made one suspicious of the presence of accessory splenic tissues.

In May 1946, the patient consulted her local doctor because of severe pain in the left side and back and was told she might be pregnant. In the latter part of April, the vaginal bleeding recurred and the fourth day after its onset, May 2, 1946, she entered the Cook County Hospital as a threatened abortion case. She was treated for shock and severe anemia by multiple transfusions of whole blood. A blood count done on May 3, 1946, revealed RBC 1.06, WBC 33,700, Platelets 252,290 and Reticulocytes 4.9. A marrow smear was reported as not unusual, and it was the impression of the hematologist that local genital pathology was the cause of the prolonged hemorrhage. On May 11, 1946, a curettement was done with negative gross and microscopic findings, and on May 22, 1946, she was operated upon and the left tube and ovary were removed. Diagnosis: hematosalpinx and hemorrhage into an ovarian cyst. No further platelet counts were done and the patient left the hospital on the twenty-ninth day.

At the present admission, she complained of pain just above the right iliac crest which was present for 4 days, and was dull and aching in character. She was awakened during this period each morning at 4:00 A. M., by a pronounced desire to defecate but was unable to have a bowel movement. Nausea and vomiting of clear fluid relieved the

urge to defecate without alleviating the pain. This sequence was repeated once each afternoon during the present illness with no relation to hour, food intake or activity. Voluntary dietary restrictions were imposed. On the day of admission, she was again awakened with the desire to defecate, but had relief following a small clear liquid emesis which this time contained specks of blood. Upon admission to the Cook County Hospital the

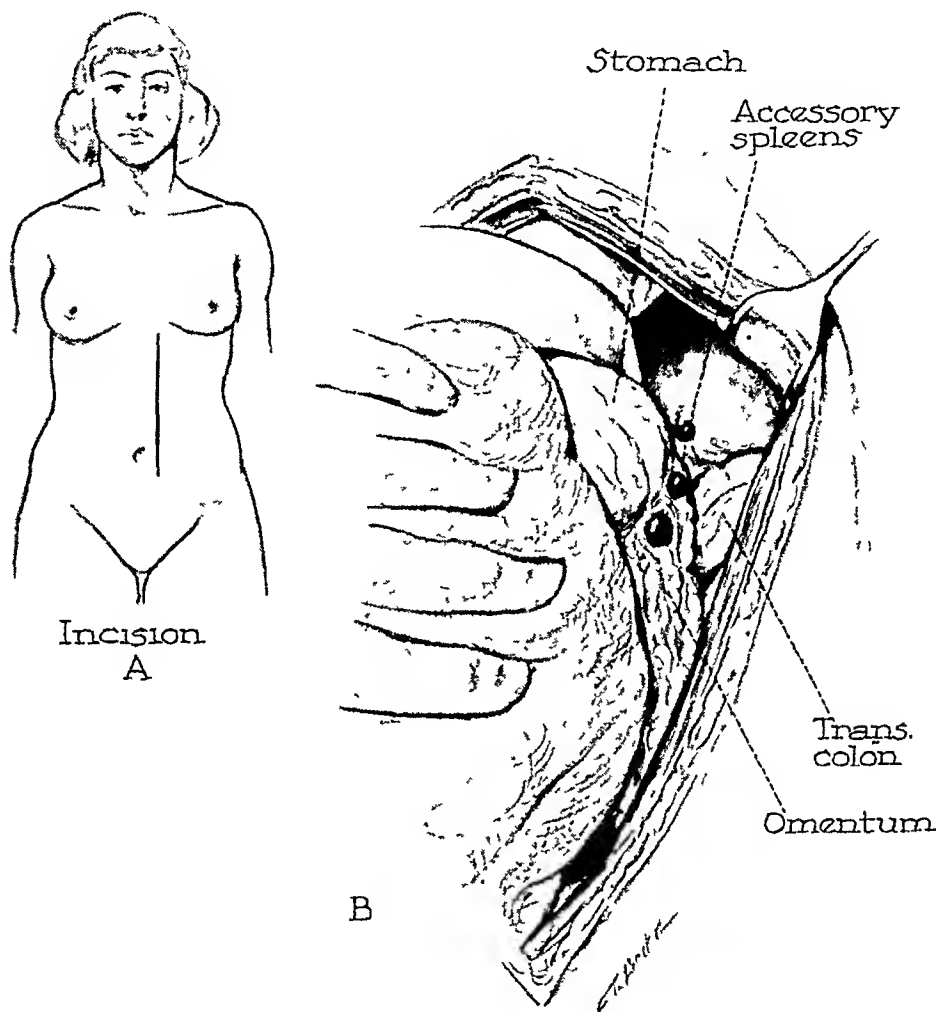


FIG. 1. (A).—Longitudinal left transrectus incision gave adequate exposure. (B).—The three accessory spleens as seen at surgery.

patient gave no history of drug or medication ingestion nor of recent illnesses. The family history was essentially negative and venereal disease was denied.

*Physical Examination.* Physical examination revealed a pale, thin white female who did not appear acutely ill. Blood pressure 110/80, pulse 90, respirations 18, and the rectal temperature was 99.8. Several large ecchymotic patches were found over the body unassociated with trauma. The abdomen was soft, not tender, and no masses could be palpated. Bowel sounds were somewhat hypo-active. Left subcostal and Pfannenstiel scars were well healed. The pelvic examination was non-contributory except for a very firm, regular cervix and vault, and adnexal adhesive distortion. A Rumpel-Leeds test was negative.



FIG. 2.—The largest of the three accessory spleens located in the omentum near the previously ligated splenic pedicle.



*Treatment.* The patient was placed on a high-protein, high-carbohydrate diet with supplemental vitamin and iron therapy. On November 27, 1946, the second day of hospitalization, a platelet count was 77,280. It was at this time that the possibility of accessory splenic tissue presented itself. On November 30, 1946, platelets numbered 6,850 and a normal cell count and differential were recorded. Vigorous intravenous therapy was started, giving at least 500 cc. of blood daily in addition to other parenteral fluids. An elimination diet was begun, all medication stopped, and the patient held in readiness for emergency exploratory laparotomy in search of accessory splenic tissue if significant increase in peripheral platelets did not occur. A sternal puncture at this time revealed a marrow with slightly increased granulopoieses and a right shift, but with megakaryocytes and eosinophiles in normal numbers; findings were compatible with the clinical diagnosis of recurrent thrombocytopenic purpura. Chest plate and barium studies revealed no pathology. Preoperative bleeding time was 8 minutes 5 seconds; coagulation time was 4 minutes 10 seconds. Elimination diet was discontinued since the thrombopenia was apparently not on an allergic basis; on December 4, 1946, the Rumpel-Leede test was positive.

On December 5, 1946, under pontacaine spinal anesthesia, an exploratory operation was performed, by Dr. P. T., through a longitudinal left transrectus incision. It was noted during the entire course of the operation that there was a marked tendency to bleed. Three accessory spleens were found (Fig. 1). The largest approximately the size of a cherry (Fig. 2), the second about the size of a pea and the third that of a pinhead. The first two were close to each other and were located in the omentum near the previously ligated splenic pedicle. The smallest spleen was found along the upper border of the tail of the pancreas. Macroscopically it was difficult to differentiate the latter from a tiny lymph node. Microscopic sections on all three specimens definitely established each as being an accessory spleen with the following description: the section revealed dilated sinusoids with a slightly hemorrhagic pulp and marked proliferation of mononuclear cells and a few polymorphonuclear leukocytes. The malpighian corpuscles were large. The pathologist concluded that these findings were in keeping with a diagnosis of thrombocytopenic purpura.

Following the removal of these masses, there was no dramatic cessation of bleeding; in fact, gingival hemorrhage of a moderate sort continued for two postoperative days despite whole blood transfusions. On the second postoperative day her clotting time was 9 minutes 17 seconds and bleeding time was 6 minutes. On the third postoperative day, all gum bleeding stopped, even though menstruation which began on December 2, 1946, continued. On the fifth postoperative day, December 10, 1946, the bleeding time was normal, platelets numbered 95,200 and the patient was up and about; menstruation ceased. Clinical improvement paralleled subsequent platelet increases and the patient left the hospital on December 21, 1946, with a platelet count of 750,000 to be followed as an out-patient.

The patient did remarkably well until January 8, 1947, when she again noted petechial hemorrhages and bleeding from the mouth. This increased in severity. She was readmitted. Repeated platelet counts varied between 0 and 14,000. She was reexplored on another surgical service January 14, 1947, and no additional splenic tissues could be found. However, on January 22, 1947, her platelet count had risen to 92,360. The patient gradually improved, her bleeding stopped and upon discharge from the hospital was clinically improved. She will be followed in the out-patient department. Whether or not tissue damage following surgery may stimulate platelet formation or not is theoretical. It seems more logical to conclude that splenic "seeding" might have occurred, or that ectopic splenic tissue still may exist in some very remote anatomical recess.

Many other methods of therapy have been advocated, especially in chronic cases, such as snake venom, cevitic acid, roentgen-ray, viosterol, parathyroid extract and rutin. but these usually fail to produce the desired results.

The treatment for purpura hemorrhagica is splenectomy. This is an emergency procedure in the acute cases, and may be elective if the condition is chronic. The possibility of accessory spleens must be kept in mind, a search made for these, and if found they must be removed. Repeated transfusions with freshly removed matched blood (not bank blood) supply effective platelets. Hemorrhagic manifestations usually disappear while the patient is still on the operating table, and the platelet count rises immediately.

## SUMMARY

1. A case of recurrent primary thrombocytopenic purpura associated with the removal of three accessory spleens is reported.
2. The literature is reviewed.
3. The importance of searching for accessory splenic tissue at the time of operation is emphasized.
4. The pathologic physiology of the spleen is reviewed.

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# STREPTOMYCIN IN SURGICAL INFECTIONS

## Part VI. Lung Abscess and Empyema\*

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THE LITERATURE ON STREPTOMYCIN in bronchial and pulmonary infections is not extensive. Good results have been reported to follow its use in infections caused by *Klebsiella pneumonia* (Friedlander's bacillus) and *Hemophilus influenzae* (Pfeiffer's bacillus) as well as in tularemic and acute tuberculous pneumonias.<sup>1, 2, 3</sup> These results have been confirmed in U. S. Army hospitals.<sup>4</sup> Bronchitis and bronchiectasis have been consistently benefited only when streptomycin has been given in combination with penicillin. In asthma associated with chronic respiratory infection a limited therapeutic trial of streptomycin has not been encouraging.<sup>4</sup>

Reports on the use of streptomycin in pleuropulmonary infections are even more limited. The Committee on Chemotherapeutics and Other Agents of the National Research Council reported its employment in five cases of non-tuberculous empyema but supplied no details except that three patients were unimproved.<sup>1</sup> The Council also reported improvement in only one of eight patients with tuberculous empyema treated by this method and concluded, on the basis of these observations, that the method was not useful. Kane and Foley<sup>3</sup> thought that the combined penicillin and streptomycin aerosol therapy of pulmonary abscess had been useful in a single case caused by *Hemophilus influenzae*. Fisher and Shaw<sup>5</sup> attributed to combined intramuscular and intrapleural streptomycin the rapid cure of a 10-year-old girl with empyema caused by *Hemophilus influenzae*. The only other report in the literature, from Buenos Aires, concerns two cases of empyema treated by intrapleural injections of streptomycin; the immediate improvement which occurred was not sustained when therapy had to be discontinued because the supply of the drug was inadequate.<sup>6</sup>

This communication, the sixth in a series dealing with the treatment of surgical infections by streptomycin in U. S. Army hospitals, is concerned with the results of this type of therapy in lung abscess and in empyema of both tuberculous and nontuberculous origin. The material, which was supplied to the Office of the Surgeon General by participating Army hospitals, consists of three cases of lung abscess, five cases of non-tuberculous empyema and nine cases of tuberculous empyema. Critical analysis of the case reports which make up this small series has permitted certain conclusions as to the efficacy of streptomycin therapy in these conditions.

### LUNG ABSCESS

**Case 1.**—A 39-year-old man, following a "head cold" of five weeks' duration, developed a productive cough, fever, sweats, and shortness of breath. He entered the hospital

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in the sixth week of his illness, during an acute exacerbation of these symptoms. Physical examination and roentgenographic studies were consistent with a diagnosis of abscess of the right upper lobe. Penicillin given intramuscularly in doses of 40,000 units every three hours and general supportive measures produced no results at the end of 6 days. On the following day thoracotomy was performed, the findings including a cavity approximately 10 x 5 x 10 cm. and a bronchopleural fistula. Open drainage was instituted and a pack was applied. Culture of the pus yielded mixed organisms, including pneumococci.

After operation penicillin was continued by the preoperative routine and was supplemented by streptomycin given in 0.6 Gm. doses intramuscularly every 4 hours. In addition, a streptomycin solution containing 2 mg. of the drug per ml. was instilled 3 times daily onto the pack in the abscess cavity; the solution was nonirritating and it seemed to reduce to a considerable degree both the odor and the amount of the drainage. The patient demonstrated progressive clinical improvement and after the fifth day had no temperature elevations. Serial roentgenograms revealed subsidence of the pneumonitis surrounding the lung abscess and a progressive decrease in the size of the cavity.

**Case 2.**—A 29-year-old man entered the hospital with a far-advanced bronchiectasis involving all the lobes of the right lung, an abscess of the right lower lobe, a severe cough productive of 75 to 150 ml. of foul sputum daily, and a 60-pound weight loss. His illness had been of two years' duration.

Inhalations of penicillin, repeated bronchoscopic aspirations, postural drainage and supportive therapy were without effect. Repeated examination of the sputum revealed numerous gram-negative organisms, but no acid-fast bacilli. Parenteral streptomycin therapy was therefore begun, with the hope of bringing about healing of the lung abscess, and 290 Gm. were given over a 76-day period. The sputum expectorated did not decrease in amount, and there was continued destruction of the lung tissue around the abscess. Death occurred three days after streptomycin had been discontinued.

**Case 3.**—A 25-year-old soldier developed extensive cavitation of the right lower lobe subsequent to pneumonitis. During 8 days of treatment with penicillin the temperature averaged 102° F. Cultures of the sputum revealed a variety of streptomycin-sensitive gram-negative bacilli and gram-positive cocci. No immediate response followed the parenteral administration of streptomycin in dosages of 1 Gm. daily, and on the fifth day of treatment roentgenograms revealed no change in the extent of cavitation. The following day, however, the patient coughed up a large amount of sanguinopurulent material and the temperature promptly returned to normal.

#### COMMENT

The role of streptomycin is difficult to evaluate in the first of these three cases, since sensitivity tests were not carried out on the bacterial cultures and penicillin was given before operation as well as in combination with streptomycin after operation. The only positive results were noted after local instillations of streptomycin, in the form of a decrease in the odor and amount of drainage. It is possible that this patient might have responded just as well if streptomycin had been omitted and treatment had been limited to surgery and penicillin. In the second case the pathologic changes, which were far advanced and of a progressive character, were not influenced by a 76-day course of streptomycin. In the third case, in which a relatively early lung abscess was caused by streptomycin-sensitive organisms, the administration of the antibiotic was possibly helpful in reversing the progress of the infection. The evacuation of pus and the subsequent alteration of the course of the disease occurred after only six days of streptomycin therapy, it is true, but it is well known that edema of the main bronchi and immediate branches may

respond favorably after only a few days of specific chemotherapy. The dosage in this case, 1 Gm. per day, is lower than the usual dosage, but was apparently adequate in this instance.

#### NONTUBERCULOUS EMPYEMA

**Case 4.**—A 26-year-old man, following a nontraumatic perforation of the sigmoid colon, successively developed peritonitis, a right-sided subdiaphragmatic abscess, and a severe right-sided empyema. When the subdiaphragmatic abscess was drained a probable intrahepatic abscess was demonstrated. Shortly afterward a massive collapse of the right lung occurred. It partially re-expanded, but the patient's condition became critical.

Culture of pus from the chest, 150 ml. of which was removed by thoracentesis, revealed *Escherichia coli* as the predominating organism. Streptomycin therapy was therefore begun, in the amount of 2.4 Gm. daily by the intramuscular route and 2.0 Gm. daily by the intrapleural route, after aspiration. The result was prompt and gratifying. The temperature, pulse and respiration fell to normal levels, there was no further weight loss, and the patient's appetite improved. By the end of 26 days of treatment his condition was sufficiently stabilized for right thoracotomy to be done, with drainage of the residual empyema. Streptomycin was continued by the intramuscular route for 8 days after operation; at the end of this time the temperature was normal. The patient remained permanently afebrile and the empyema cavity ultimately was obliterated.

**Case 5.**—This patient, a 24-year-old man, required thoracotomy with open drainage for a right-sided empyema following peritonitis of appendiceal origin. Cultures of the pus from the chest grew mixed aerobic and anaerobic gram-negative rods and gram-positive cocci, all of which were susceptible to streptomycin. After operation penicillin in dosages usually adequate (320,000 units per day) failed to produce the usual results, and on the fourth postoperative day streptomycin, in dosages of 3 Gm. daily, was added to the therapeutic regimen. Progressive improvement occurred and was sustained when therapy was discontinued at the end of 13 days. At the end of 2 weeks the temperature was normal and the empyema cavity, which had become greatly reduced in size, was continuing to close rapidly.

**Case 6.**—A 21-year-old soldier, who sustained a penetrating pistol shot wound of the left chest, with hemopneumothorax, had been treated overseas with intercostal tube drainage, supportive therapy, and 30,000 units of penicillin intramuscularly every 3 hours. In the Zone of Interior cultures from the lesion revealed staphylococci and *Klebsiella pneumoniae*, both of which were sensitive to streptomycin. Roentgenograms showed two distinct pockets of fluid.

Penicillin was administered in adequate dosages for 2 weeks, without demonstrable clinical response. Streptomycin was then added to the regimen in the amount of 1.2 Gm. daily by the intramuscular route. In addition, daily thoracenteses were carried out in the pockets not drained by the intercostal tube and were followed by instillations of 200 ml. of a solution containing 0.5 Gm. of streptomycin and 40,000 units of penicillin. The response was dramatic clinically as well as bacteriologically. On the second day of treatment the aspirate grew only *Staphylococcus aureus* and on the fourth day it was clear and sterile. There was no temperature elevation after the fourth day. Intramuscular injections of both antibiotics were continued for 7 days and intrapleural injections for 10 days. The fluid in the chest became progressively clearer and scantier, and at the end of 2 months was completely absorbed.

**Case 7.**—An 18-year-old soldier with unresolved pneumonia of the left lower lobe on a bronchiectatic basis developed an acute sacculated empyema of the left pleural cavity with a pronounced constitutional reaction. Aspiration yielded thick greenish-yellow pus from which streptomycin-sensitive *Hemophilus influenzae* and anaerobic nonhemolytic streptococci were grown.

Penicillin and sulfadiazine were both ineffective. Streptomycin (0.5 Gm. by the intramuscular route) was then given every four hours for ten days. At the same time, an

attempt was made daily or every second day to empty the various loculated empyema cavities and to replace the aspirate with 0.25 Gm. of streptomycin in solution. For 3 days after this treatment was begun the temperature was lower and the patient improved appreciably. Then drainage of the pockets by aspiration became increasingly difficult and the temperature returned to its formerly high peaks. Eventually the cavity was completely obliterated by thoracotomy with open drainage, under cover of parenteral penicillin and streptomycin. Three months later a plastic operation on the chest wall was carried out, and the soldier was in good condition when he was subsequently separated from Service.

**Case 8.**—A 38-year-old man, first seen in June, 1947, had a persistent empyema cavity as the result of a shell fragment wound in 1944. A thoracotomy and several thoracoplasties had been ineffective. In July, 1946, decortication of the empyema space was followed by a breakdown of the wound, which eventuated in a saucerized cavity and the exposure of a large area of visceral pleura. Hemolytic *Staphylococcus aureus* infection was persistent and the course was septic. An attempt at a split thickness skin graft was not successful.

In July, 1947, culture of material from the empyema cavity again yielded hemolytic *Staphylococcus aureus*, which was now resistant to penicillin. The organism was, however, sensitive to streptomycin, which was given in dosages of 2 Gm. daily by the intramuscular route. The temperature almost immediately returned to normal and the amount of drainage decreased. The cavity was then packed with gauze saturated with 1 Gm. of streptomycin in physiologic salt solution, and several negative cultures were secured over a 10-day period. It was now possible to carry out decortication of the visceral pleura, a plastic operation on the thoracic muscles, and closure of the chest wall. The wound healed promptly and firmly and the patient was in good health when he left the hospital after operation.

#### COMMENT

In this group the two patients with empyema complicating peritonitis of fecal origin undoubtedly derived a beneficial cumulative effect from streptomycin-penicillin therapy employed as an adjuvant to adequate surgical drainage. In Case 4, in fact, streptomycin therapy was probably life-saving. In Case 6, in which the empyema originated in a combat injury, the results were equally good; the elimination of streptomycin-sensitive organisms and then of penicillin-sensitive staphylococci might not have been achieved had either antibiotic been employed singly. Case 7 emphasizes the difficulties and unwisdom of attempting to manage a loculated empyema cavity without adequate surgical drainage. Streptomycin was not effective, and could not have been expected to be effective, until thoracotomy had been carried out. Case 8 illustrates radical curative surgery which was made possible by the judicious local application of streptomycin. The systemic use of the antibiotic would not have been effective alone in this case since bacteriostatic concentrations by way of the blood stream are not achieved in fibrotic, poorly vascularized tissues. In this case the indications for streptomycin therapy were clear-cut, as the staphylococci had lost their susceptibility to penicillin.

#### TUBERCULOUS EMPYEMA

Streptomycin was tested in Army hospitals in nine cases of tuberculous empyema, six of which were treated by surgical measures also. One of the patients treated only by medical measures had advanced chronic pulmonary tuberculosis of all lobes of the left lung, a right bronchopleural fistula, and a mixed tuberculous empyema for which open thoracotomy had been done. The

daily dosage of streptomycin consisted of three Gm. by the intramuscular route, with an additional one to two Gm. directed through the thoracotomy wound by means of the aerosol spray. The first response was encouraging. Over a period of two months drainage decreased, healthy granulations developed around the wound, and the fistula closed. The fistulous tract, however, reopened within the month, in spite of continued treatment, and the exudate was found to contain acid-fast bacilli. Streptomycin was discontinued at the end of five months, after a total of 600 Gm. had been given, when it appeared obvious that it was accomplishing nothing.

The two other patients treated by medical means each received two Gm. of streptomycin daily by the intramuscular route, supplemented by numerous instillations of one Gm. or more of streptomycin solution into the pleural cavity after aspiration of the fluid. Each of the patients had tuberculous empyema and a bronchopleural fistula secondary to moderately advanced pulmonary tuberculosis. At the end of 120 days of treatment there was no clinical improvement in either case and roentgenograms revealed that the parenchymal lesions had not been favorably influenced.

Two of the six patients treated by surgical measures had been submitted to closed tube drainage. Each received 87 Gm. of streptomycin by the parenteral and pleural routes over a period of 55 days. The first patient was not only unimproved, but was actually worse at the end of the therapeutic trial. The second, whose tube was removed, showed no improvement until penicillin was combined with the streptomycin solution which was instilled intrapleurally after straphylococci had been isolated from the exudate. After 15 days of the combined treatment all thoracenteses were dry.

In four cases of tuberculous empyema streptomycin was used as an adjuvant to extensive surgery, as follows:

**Case 9.**—A 38-year-old negro man with moderately advanced tuberculosis of the right lung developed a mixed tuberculous empyema of the right pleural cavity. Examinations of the sputum were consistently negative for acid-fast bacilli but cultures from the empyema cavity were positive on several occasions, and were also positive for hemolytic *Staphylococcus aureus*. After the cavity had been unroofed and exteriorized, roentgenograms showed another large pocket in the right hemothorax; the parietal pleura was greatly thickened and the right lung was compressed to about a quarter of its normal volume. Penicillin by the parenteral route and azochloramid used locally were not effective, but over the next four months, under the influence of bed rest and supportive therapy, the temperature gradually fell to 99° F. Thoracoplasty, followed by two revisions, failed to eradicate the infection and close the cavity.

Two months later, when the patient began to expectorate rather large amounts of frothy sputum, repeated examinations of the sputum were still negative for acid-fast bacilli. Streptomycin therapy was instituted at this time, and 2 Gm. were given daily for 185 days. The patient's cough decreased and became less productive, drainage from the empyema stoma became negligible, his general condition showed progressive improvement, he began to gain weight, and the residual fistula eventually closed. The final roentgenogram showed the left lung clear, while on the right there was complete compression of the entire lung field, with no evidence of any empyema space.

**Case 10.**—A 31-year-old man with far advanced chronic active pulmonary tuberculosis of the upper left lobe, associated with cavitation and left tuberculous empyema, was submitted to thoracoplasty in March, 1943. He was readmitted to the hospital in 1946 because of residual cavitation in the left upper lobe, under the thoracoplasty. Lobectomy

had been contemplated, and in preparation for the operation streptomycin was given parenterally in a dosage of 2 Gm. daily for 98 days, but six weeks after antibiotic therapy was begun the empyema cavity was merely unroofed and a revision thoracoplasty was carried out. Cultures were negative for pyogenic organisms but positive for acid-fast bacilli.

Repeated aspirations of the empyema cavity were done after operation. The fluid gradually decreased in amount and became thinner, and the space was dry within about 6 weeks. Roentgenograms showed satisfactory collapse of the cavity. The patient was now symptom-free and there was no evidence of a spread of the disease to the unaffected lung.

**Case 11.**—A 38-year-old man with chronic active pulmonary tuberculosis of the right upper lobe was admitted to the hospital with a mixed right tuberculous empyema a month after a second-stage thoracoplasty. Culture of the exudate yielded hemolytic *Staphylococcus* and acid-fast bacilli. Aspirations every two days combined with penicillin replacement therapy produced no results, and it was decided that another stage thoracoplasty would be necessary to collapse the empyema cavity. This was done after streptomycin had been given intramuscularly in 2 Gm. doses for 115 days. After operation the empyema space was aspirated 3 times weekly, from 50 to 100 ml. of fluid being withdrawn each time. An anterior fourth stage thoracoplasty was performed 17 days after the third stage. The wound healed per primam. Aspirations of the cavity returned dry on the 39th day after operation. Repeated sputum examinations were negative for acid-fast bacilli, and there was no apparent spread of the tuberculous lesion to the intact lung.

**Case 12.**—A 30-year-old man was admitted to the hospital with numerous draining pleurocutaneous tuberculous sinuses. Thoracotomy had been necessary for a penetrating wound of the right chest and tuberculosis was later found to be responsible for the persistent drainage, which had not been checked by several revisions of the thoracotomy and by decortication. Although unroofing of the cavity resulted in a decrease in its size, the sinuses remained open. Streptomycin was then given daily for 60 days in 2 Gm. doses. After 5 weeks of therapy the sinuses closed completely and remained closed when the antibiotic was withdrawn 25 days later.

#### COMMENT

The three cases of tuberculous empyema treated only by medical measures make clear that streptomycin is not of value in chronic productive tuberculosis. They also make clear that bronchopleural fistulas and empyema of tuberculous origin will not improve under this form of treatment if parenchymal lesions remain unimproved. In one of the cases treated by closed tube drainage the patient became worse under streptomycin therapy, but the other, similarly treated case illustrates the advantages of combined therapy, which were also apparent in the case of nontuberculous empyema treated by both penicillin and streptomycin (Case 2).

In the first of the four cases in which streptomycin was used as an adjuvant to extensive surgery (Case 9) the closure of the residual fistula could be attributed not only to the consequence of compression of the parenchymal lesion but also to the direct bacteriostatic action of the drug on the offending bacteria. In the second case (Case 10), in which the empyema was of purely tuberculous origin, it would seem that streptomycin was of value in changing the character and consistency of the exudate, thus permitting a rapid obliteration by the surgery employed to bring about collapse. In the third case (Case 11) streptomycin made possible the treatment of a mixed empyema as a purely tuberculous empyema; good results were obtained by aspirations and surgical collapse. In this case streptomycin was administered only by the

intramuscular route. In the fourth case in this group (Case 12) streptomycin was also administered only parenterally, but its effect on the underlying focus was apparently such that residual fistulas were obliterated.

The series, small as it is, permits a preliminary definition of the uses of streptomycin in pulmonary tuberculosis complicated by empyema: 1. Streptomycin by the intramuscular or the intrapleural route or both may suppress the pyogenic organisms in a mixed tuberculous empyema and permit the case to be managed as if it were a purely tuberculous empyema. It may be advantageous, however, to add penicillin to the therapeutic regimen, to obtain an immediate, maximal suppression of the secondary invaders. 2. The bacteriostatic effect of streptomycin in an open, mixed tuberculous empyema affords protection during extensive plastic maneuvers. 3. The use of streptomycin apparently is bringing about an extension of the scope of surgery in mixed tuberculous empyema by permitting a direct attack upon the visceral fibroplastic membrane. 4. The drug is of no apparent value in the parenchymal lesion of chronic productive tuberculosis complicated by empyema.

The subject has been adequately discussed elsewhere<sup>7, 8, 9</sup> and need not be elaborated here, but it should be emphasized again that caution must be exercised in the employment of streptomycin over prolonged periods, because of possible untoward effects, particularly on the eighth cranial nerve.

#### SUMMARY

Experiences in U. S. Army hospitals with streptomycin as part of the therapeutic regimen in lung abscess, nontuberculous empyema, and tuberculous empyema have been presented. The series of 17 cases is too small to permit conclusions, but certain of the results are sufficiently encouraging to warrant continued use of this method on the proper indications.

NOTE.—The authors acknowledge with thanks the cooperation and helpful suggestions of Dr. L. M. Shefts, Consultant in Thoracic Surgery, Brooke General Hospital, in the preparation of this paper.

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MEMOIR  
ENRIQUE FINOCHIETTO, M.D.  
(1881-1948)

It is with sincere regret that the ANNALS OF SURGERY announces the death of Dr. Enrique Finochietto on February 17, 1948. His passing, in his sixty-eighth year, represents an irretrievable loss to the medical profession not only because a brilliant and inquiring mind has been silenced forever but also because the technical investigations which he and his brother, Ricardo, were



Dr. Enrique Finochietto

conducting at the time of his death have been left unfinished; these encyclopedic studies, which were eventually to be published in 16 volumes, represented years of untiring research.

Born on March 13, 1881, in Buenos Aires, Dr. Finochietto received his medical degree from the School of Medicine of the University of Buenos Aires in 1904. In 1906 he was appointed to the staff of the Rawson Hospital, in whose corridors his was a familiar figure during the remainder of his life. His gradu-



ate medical training took him not only to Europe but also to the United States, where he worked with Erdman and Harvey Cushing.

For his service *ad honorem* at the Argentine Hospital in Paris during World War I he received the Legion d'Honneur. Elected president of the College of Surgeons of the City of Buenos Aires in 1922, he also officiated as president of the Fifth Argentine Congress of Surgery. He was a member of the Academies of Surgery or Medicine of Argentina, Madrid, Bolonia, Montevideo, Paris, Rio de Janeiro, and La Pas, Bolivia.

Although Dr. Finochietto attained international recognition as a teacher, surgeon, and inventor, he remained modest and retiring. The numerous surgical instruments and appliances which he invented found universal application. His didactic methods were applauded all over the world. Ever conscious of the weighty responsibility of his profession he would frequently quote Faure:

We live under the most extraordinary emotional circumstances.

Life or death depends on us every day. A hint, a passing inspiration during a difficult operation, a gesture, a furtive look, might mean life or death. We all have this same conviction but nevertheless we never retreat before such a terrific responsibility.

He unselfishly devoted his life to the good of mankind, with complete disregard for material benefits. Only recently he financed the complete re-equipping of his operating theater at Rawson Hospital. Probably the greatest tribute which could be paid to his technical surgical skill was paid by Lord Moynihan, president of the Royal College of Surgeons, who said, after witnessing Dr. Finochietto perform an operation, "If ever I have to be submitted to the knife, let it be by this extraordinary surgeon called Enrique Finochietto."

Scientist, inventor, preceptor, surgeon, and indefatigable worker, he has left to mankind a memory of service which will be difficult to duplicate but which will serve as an inspiration to all who follow him.

—MICHAEL E. DeBAKEY.

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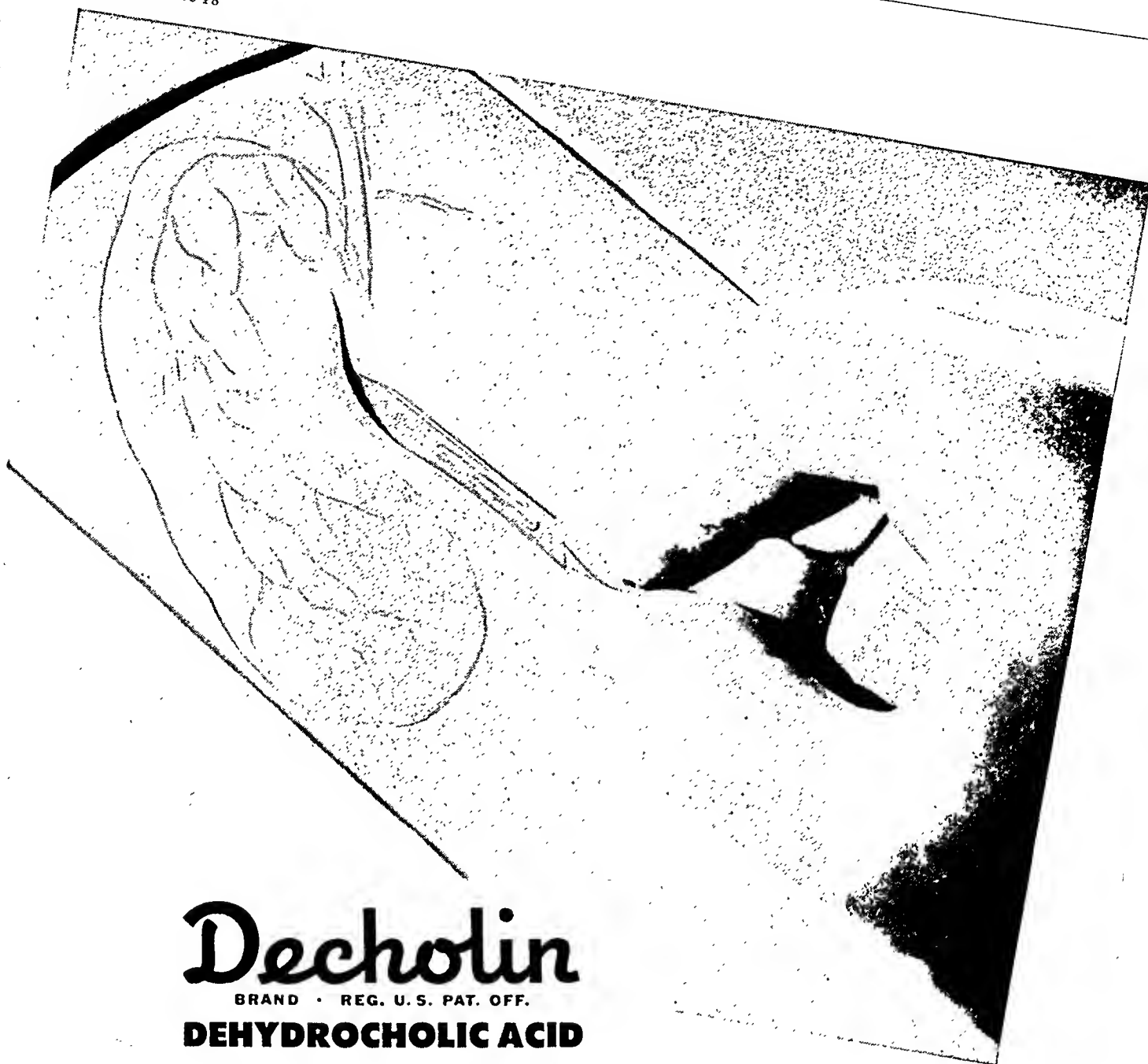


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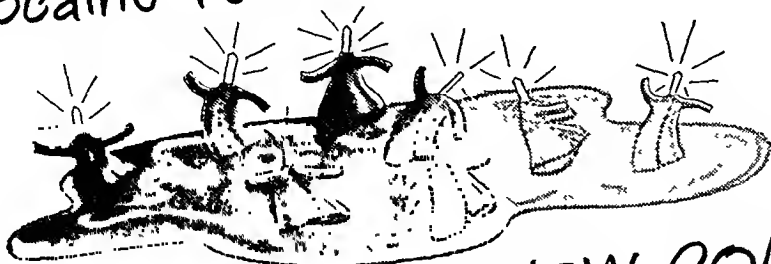
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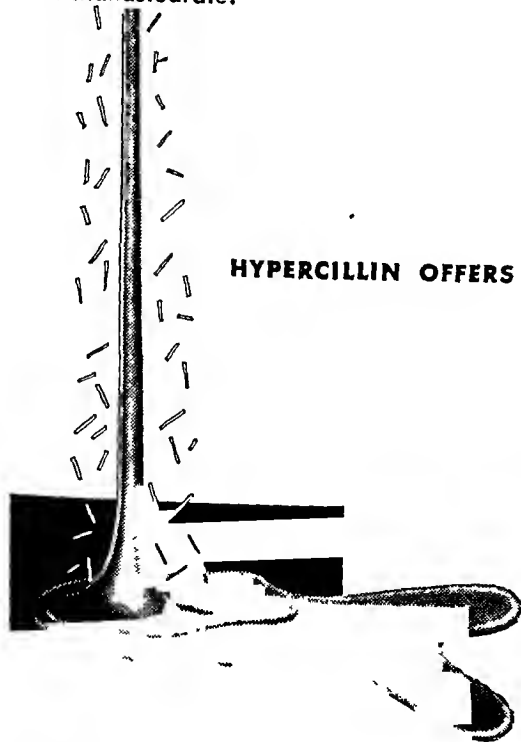
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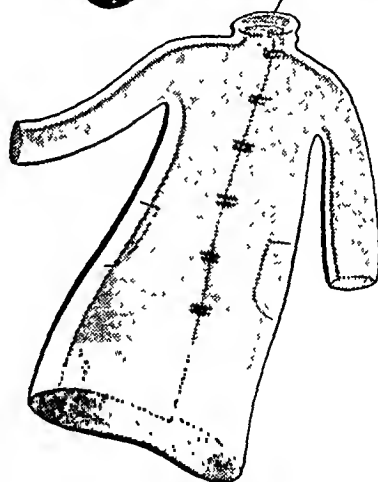
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## TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION

MEETING HELD AT QUEBEC, CANADA, MAY 27, 28, 29, 1948.

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### ADDRESS OF THE PRESIDENT HE SHALL HAVE A NOBLE MEMORY\*

WILLIAM E. GALLIE, M.D.  
TORONTO, CANADA

Article II of the Constitution of the American Surgical Association reads as follows:

"The object of this Association shall be the cultivation and improvement of the science and art of surgery, the elevation of the medical profession and such other matters as may come legitimately within its sphere."

In his presidential address in 1937 Dr. Evarts Graham put into the mouth of our founder, Dr. Samuel Gross, certain words that have interested most of us ever since. He said "I also imagine that probably you have a standing committee working on the various problems concerned with the teaching of undergraduate surgery and with the later years of special training which you mentioned earlier. It is easy to see how this Association through a distribution of pamphlets on these subjects from time to time must hold the position of leadership in these important aspects of surgery which the founders dreamed for it." Well, there is no doubt that this Association has had much to say about graduate training in surgery and has taken a leading part in the wonderful transformation that has taken place in it. It is not so clear, however, that we have given the attention that our founder had in mind to the teaching of the undergraduate.

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\* Read before the American Surgical Association, Quebec, Canada, May 27, 1948.



In our meeting in Boston in 1935 you may remember that we had a symposium on the teaching of surgery in which Archibald, Cutler, Heuer and Whipple were the chief contributors and which was followed by a tremendous discussion by Bevan, Orr, Lewis, Pool, Rodman, Graham, McClure and myself.

This discussion was of great importance for it led to the extraordinary improvement in the quality of the training of surgeons and of surgical specialists that made itself so obvious during the War and is now showing its beneficent effect in civilian life.

The discussion of undergraduate teaching, however, was much less productive as there seemed to be a general feeling that conditions were pretty satisfactory in most of the medical schools. It was agreed that the urgent need at the time was an improvement in the graduate training of the surgeon with the establishment of higher standards. It was hoped that the day would come when the minimal standards set up would be required for licensure to practise.

But now that the programme for graduate training in surgery has been generally accepted it seems to me that we should go back again to the suggestion made by our founder and examine more carefully the teaching of the undergraduate. It is quite possible that the establishment of the training of the surgeon as a postgraduate study may have some effect on what the undergraduate should be taught.

As the years have rolled around tremendous changes have occurred in surgery which have caused equally tremendous changes in our curricula. When I was a student I had two bedside clinics and one didactic lecture a week extending over two clinical years of 30 weeks each. This covered the whole range of surgery exclusive of the eye, ear, nose and throat. Then gynaecology separated off and was awarded special clinical and didactic hours and almost immediately this same thing happened with urology. Then came orthopedic surgery, neurosurgery, and plastic surgery, each with its own specialists and each requiring a place in the curriculum. The result was the addition of a third clinical year. Now come thoracic surgery, vascular surgery, cancer surgery, and what not, all requiring special curricular arrangements. The result is that ten times as much space is given to the teaching of surgery as was given in 1903.

Now this is the phase of medical education that I wish to analyse. First of all, why do we teach all this surgery to medical students? Is it that conditions today are as they were 40 years ago and that every graduate must be taught enough surgery to enable him to carry out the less difficult operations that are indicated in general practice? Or is it that we have not made the changes in our curricula that our greatly changed policy in regard to surgery demands. This Association and all other national associations along with the American and Canadian colleges are committed to the principle that major surgery shall be done only by those who have been adequately

trained for it. For the young men and women who wish to do surgery today we are demanding five years of postgraduate supervised training plus the passing of stiff examinations. Then why teach the enormously increased amount of surgery of our present day curricula to thousands of medical students who are going to be physicians or public health officers or ordinary general practitioners? As far as the latter are concerned, I suggest that it is not only unnecessary but it is actually dangerous, for as long as our state and provincial licensing boards continue to grant the right to practise surgery to untrained men, as they do today, this half-baked undergraduate training is a temptation to less scrupulous practitioners to do what they ought not to do. It actually tends to perpetuate the evil which our program of graduate training is trying to end.

It is not for me to tell you how to overcome this anomalous situation whereby, as Elliott Cutler has said, the American public may legally be cared for, indeed subjected to a dangerous surgical procedure by a student who has just graduated from medical school. As far as my own country is concerned, however, I propose to devote much of the remainder of my life to an effort to provide enough properly trained surgeons to take care of our people and to preventing those who are not so trained from having a part in it.

The answer, of course, is that we should review our curricula in the light of the changes that have occurred in surgery and of the new policy we have adopted towards it. The time has now come when the study of surgery must be established as a postgraduate course with not only the apprenticeship in hospital but also a special curriculum of studies covering surgery itself and all the appropriate basic sciences. In the undergraduate years it should be reduced to what might be described as an introduction to surgery with special emphasis on applied anatomy, physiology and pathology, on methods of examination and on the diagnosis of those diseases and injuries that are ordinarily found in the Department of Surgery. I am suggesting, indeed, that the teaching of such subjects as peptic ulcer, carcinoma of the stomach, tumour of the brain, bronchiectasis and dozens of others should be either conducted by the physicians or if by us, then as physicians and not as surgeons. Our time will come when the young graduate is definitely committed to the program which we have agreed is necessary for the training of a modern surgeon.

Since I have been turning this subject over in my mind I have found a tremendous variation in the curricula of the schools scattered over the country. A survey made recently by the orthopedic surgeons showed a total lack of unanimity in regard to what should be taught and the same thing seems to be true of all the specialties and, indeed, of general surgery itself. In some schools each specialty is an entirely separate department which has no integration with the other departments except through the dean. The result is repetition, neglect of general fundamental principles and gross waste

of time. And even in schools where the surgical specialties are sub-departments of general surgery the tendency is to teach the specialty rather than the simple fundamentals. Indeed, it has been my observation that quite frequently the members of the various special departments are neither interested in nor capable of teaching the applied physiology, biochemistry, and pathology which must be mastered by the undergraduate in order that he may understand disease.

Along with the growth of surgery has come a corresponding increase in the size of the textbooks. As a Professor of Surgery I must have a dozen different textbooks entitled 'The Principles and Practice of Surgery' all sent by the publishers in the hope that they would be recommended for the students. The preface in each case states that the book was written especially 'for students and practitioners'. Now as far as the undergraduates are concerned the 14 or 15 hundred pages in these books are about three times too many and for the practitioners, that is the surgeons, they are not nearly enough. It seems to me that a textbook for undergraduate students should be limited to 'principles' and should contain only minimal reference to 'practice'. What the student needs is help, both from his instructors and from his textbooks, in the art of examining the patient and eliciting and interpreting physical signs; help, too, in understanding the underlying pathology and linking it up with the history, the symptoms and signs, the probable diagnosis, the prognosis and the indications for treatment. The actual 'practice' is something for postgraduate study.

Now I am perfectly aware that the views I am expressing here are highly controversial and will probably be irritating to many of us who have school organizations that have received my criticism. To them I offer my humble apologies and present as an excuse my own feeling of uncertainty and my sincere desire for the help of all who think of these things, to arrive at a good solution. It is my hope that at some time during this meeting this Association will see fit to appoint a committee to make a survey of the whole subject of undergraduate teaching of surgery in America and elsewhere and to bring in a report on some future occasion which will give us a true picture of conditions as they are at present and as we would like to see them in the future.

It is my thought that this survey should cover the principal schools of America and Europe and that it should be based on visits to these institutions as well as on questionnaires. Such a survey would not be aimed at making comparisons of one school with another but would be directed solely towards finding out what is best in each in order that we may be in a position to do what Dr. Gross thought we should be doing in regard to the undergraduate teaching of surgery.

The second problem I wish to discuss is that of the full time professorships in surgery. It is just 20 years since I accepted such an appointment

and as I have been interested not only in my own difficulties but also in those of other full time professors I am in a position to make some comments.

First of all let me assure you that I have no regrets and that I would do it again without the slightest qualm. The organization of a school for surgeons was what I wanted to do more than anything else and it couldn't be done except on some sort of full time basis.

It should be appreciated, however, that it cannot be done without a great financial sacrifice. Unless the satisfaction that the professor gets out of his position and out of the opportunities which his position affords him is sufficient to outweigh the loss of private income he should not accept the appointment. There isn't the remotest possibility for a first-class professor to command an income either from his salary or from a limited amount of consultation practice, comparable to what he could expect from private work.

Again, when a professor accepts a full time or a modified full time appointment he should be assured of an adequate pension when he retires. I have no personal cause for complaint in this regard for although my pension is only a token yet this was compensated for by an arrangement whereby my retiring time would be at the age of 65 instead of the regulation 60. Whether retirement comes, however at 65 or 60 there should be an adequate pension for there isn't a chance in the world, no matter how distinguished and accomplished the professor may be, of picking up private practice again in competition with the young men he has trained. This business of dropping a professor of surgery at 60 or thereabouts without an adequate pension is sure to prevent us, in the long run, from getting the best men for the full time chairs.

The selection of the Professor of Surgery, next to that of the Professor of Medicine is the most important duty of the Dean. Having in mind that the most important duty of a professor is the training of surgeons, I would recommend to the Dean that he select as Professor of Surgery a first-class surgeon who can command the respect and admiration of his students. There is nothing sadder than to see a great chair occupied by a well meaning man who arouses in his colleagues and students a feeling of pity. If I were a young fellow again embarking on a surgical training I would pick out for my teacher one of the young professors in this society, particularly one with a stimulating personality, an enquiring turn of mind, and a background of training and performance that left no doubt that he was a good surgeon. Indeed, I expect that is what we all did.

The point, however, that this professor must be a first-class surgeon calls for comment. I note a tendency from time to time to appoint as professors men who are so young that they have never been heard of as surgeons. They may have had excellent training in hospital and laboratory, they may have done good research work and they may be good lecturers and clinicians but is there any certainty that they are really good surgeons? Would you

have them make the decision and carry out the treatment if you were desperately ill? It is considerations such as these that make me think that the new professors should not be selected from those who have recently completed their training but rather from those whose early maturity has confirmed the promise of their youth.

I hope these remarks will not be considered reactionary for I am in hearty sympathy with the modern tendency to require in professors a broad training in physiology and biochemistry and an ability to use it in surgical research. All I am doing is making the selection of the professor more difficult by demanding that he be also a good surgeon.

The question of whether the professor shall be selected from the surgical specialists or from the so-called general surgeons, whom the specialists refer to as specialists in the small part of surgery that is left to them, namely the abdomen, thyroid and breast, is a difficult one. Many of the chairs of surgery in America have been and are occupied by most distinguished specialists. It is my impression, however, that unless such professors revert to the general surgery from which they came, they cannot give the leadership of the whole department that their position demands. They often act simply as chairmen of the department and exert their influence in an executive way rather than by leadership. While there is no harm in a professor knowing a great deal about some small part of surgery, it is equally essential that he know a great deal, or at any rate, a considerable amount about all branches of surgery.

This means, (if it is true) that the professor must be very specially trained. Not only must he have had adequate experience in anatomy, physiology and biochemistry, preferably with research experience in at least one of them, but he must have had a very broad training in surgery itself, including neurosurgery, orthopedic surgery, urology, thoracic surgery and so on, and he must be competent to discuss the general problems that arise in each. It begins to look, therefore, as if the candidates for the chairs will have to plan their training a long way back and with academic life definitely in mind in order that they may have the broad education that their position requires.

Looking over the field in America and Great Britain it seems to me that the places where the so-called full time professorships have worked best are those where the professor is also surgeon-in-chief of the hospital. Under such circumstances, if he is the ideal man for the appointment, the whole surgical service will have the benefit of his leadership and the school and the hospital will work as a unit. In those instances where the professorial unit comprises only one of several surgical services, and is on an equal basis and in competition with them, there is unhappiness and often bitterness. The professor and his full time staff, on salaries of a certain amount, look on their colleagues on the other services as rolling in wealth and the effect is demoralizing. The other services respond by belittling the professorial

service as composed of men who can face only a protected existence and could not compete in the open market. And so it goes. After looking them all over I wouldn't accept a chair of surgery unless it carried with it the post of a surgeon-in-chief of the main university hospital.

Looking back over the years of the full time professorships in America I would say that they have come to stay. You cannot run a first class school and particularly a first class postgraduate school for surgeons without them. To make the show go the professor must be on the job morning, noon, and night. He must teach and he must teach others to teach; he must operate and he must teach others to operate; and he must lead in research and act as a constant liaison with all the research departments. When you add to this the never ending rounds, staff meetings, committee meetings, and everything else it is easily seen that the day of the old time professor with the large private practice is over.

On the other hand the experiment of the full time professorship, in spite of the difficulties that have been encountered, has worked amazingly well. Under this system the departments of surgery have flourished; research, as evidenced in our program to-day, has taken on a new life; and schools for the training of surgeons have sprung up everywhere. Indeed the chief accomplishment of the full time professor up to the present has been the establishment of our modern system of graduate training for surgeons. The standards which have been set up by the Colleges of Surgery and the various Boards have been accepted by the schools and there is little doubt that the quality of the candidates for fellowship or for certification is being steadily improved.

The setting of high standards, however, brings with it the necessity for special instruction. It wasn't long after the establishment of the Royal College examinations in Canada that a demand arose for refresher courses and special instructional classes that would prepare the candidates for the examinations. At first these were conducted extramurally by private arrangement, but more recently the universities have recognized their responsibility and have established postgraduate curricula for the residents and assistant residents in training. These graduate students, in addition to their routine work in the hospital, now take regular courses in anatomy, physiology, biochemistry, pathology and surgery.

Placed as we Canadians are in close relationship both to the British and to the Americans, we are in an excellent position to observe the working of each system. I am of the opinion that the English students going up for their fellowship examinations are infinitely better prepared in the basic medical sciences than are ours. On the other hand they have had nothing like the practical supervised hospital training that our men have had. In our recent visit to England, however, we found that full time professorial chairs are being established all over the country and that plans are being laid for adequate graduate training comparable to

the system here. I wish I felt sure that we were as aware of the weak spot in our system, that is, in the basic sciences, as the English are of theirs.

You will recall the brilliant address of our president, Dr. David Cheever, when he drew attention to the fact that the teaching and the study of anatomy on this side of the Atlantic had fallen on evil days, was largely in the hands of Arts professors and from the standpoint of the surgeon had suffered a complete eclipse.

Well, what have we done about it? Serving as I have on the Committee on Graduate Training in the American College of Surgeons I have heard a lot of chatter about adequate training in the basic sciences, but I haven't heard much about our residents going back to the dissecting room to learn their anatomy properly. Until they do I am perfectly sure they will not be able to make a first class physical examination. The surgeon, when he looks at a limb, an abdomen, or a neck, should be able to see right through it.

The remedy, it seems to me, is twofold. First, we should require the candidates for fellowship or certification to pass a stiff examination in all the basic medical sciences as well as in surgery. Second, we should plan the four or five years of internship so that the students can receive such really first class instruction in these subjects that they can face the examination with equanimity.

When I began thinking over what I might say that would be of interest to the Association I fully made up my mind that a serious discussion of a scientific subject by an old fellow who is looking mostly on the past would be out of place. However, knowing as I do that the younger members come here to learn scientific surgery and not to discuss medical education I have decided to close my address in a lighter vein with some observations calculated to wake them up and perhaps to irritate them.

First of all I wish to suggest that surgeons as a class are grossly unscientific. When one remembers that our daily work involves the health and indeed the very lives of our patients is it not appalling that it takes us so long to learn the truth about anything? Take, for example, the surgical treatment of duodenal ulcer. Forty years ago the first gastroenterostomy was performed. Within a decade, through the influence of a few strong personalities it swept over the whole world and hundreds of thousands of patients were submitted to it. It took us twenty more years to find out that it was all nonsense. And why? The answer is, failure to study the effect of the operation on animals, failure to conduct adequate follow up studies on patients and failure to try to understand and to apply the simple rules of statistics. Let me suggest that each of us take the current issues of the best known surgical journals and see how many of the papers are based on anything but wishful thinking.

I bring the subject up in order to introduce my pet hobby of the use of foreign bodies in surgery. Please do not think that I am objecting seriously

to their use, for the largest part of my practice nowadays consists of taking them out. I simply want to draw your attention to our gross neglect of the scientific method.

A review of all the operations involving the introduction of foreign bodies would fill a book. Murphy's button, McGraw's ligature, vitallium bile duct tubes, have all given place to more physiological procedures designed to imitate as closely as possible the normal. Lane plates, vitallium plates, and now tantalum plates each have their proponents and each have their proportion of disastrous results. Stader splints, Roger Anderson pins, Smith-Petersen nails, icetongs, Steinman pins, Kirschner wires, Parham bands, and Kunscher nails have all given rise to special surgical techniques designed to undo the harm they have done. Some of them, such as the Steinman pin or Kirschner wire through the os calcis can cause an osteomyelitis of the body of that bone that we haven't yet learned how to cure. Then there are the silver plates, gold plates, celluloid plates, acrylic plates and tantalum plates used in the repair of defects in the skull. Each has been strongly advocated in our surgical journals without a shred of scientific support, except that the patients seem to survive the operations. And besides all this we have the never ending squabble about sutures—silk threads, linen threads, cotton threads, and catgut, each surgeon thinking that the reason his results are so much better than he expected is because of his special material or of the way he uses it. And now we are in the midst of the steel wire era. This is particularly annoying to me because in dealing with the postoperative hernias which result from the use of these cutting sutures I invariably spoil the edges of my knives. The other day I saw a man with an infected finger which had resulted from a puncture by the end of one of these wires which had worked its way out of a recent hernia wound and got mixed up with the contents of his trousers pocket.

Seriously, however, the matter does call for some consideration. I am not one to condemn *holus bolus* the use of foreign bodies in surgery for I know full well that great advances have been made because of them. And often enough, as in the case of the Murphy button, the combination of the good and the harm that they did has led to a really successful solution of a difficulty. On the other hand, the complications, the failures, and the actual disasters that have attended their use have been so universal that there isn't any question we should pause before using them. If it is obvious that to do a great good we must do a little harm then we must go ahead and do it, but if the desired result can be obtained without the risk attending a little harm then we should by all means avoid it. It would seem particularly important that when the ingenious surgeon feels the urge to add some new foreign body to our armamentarium he should pause and see whether he cannot then and there figure out the physiological procedure by which his bright idea, if it really is a good one, will surely be replaced.

I said a moment ago that we are very unscientific. I had in mind the



abandon with which we try out new ideas on patients without studying the results on animals; and also our naivety in thinking that an experience of a few cases justifies final conclusions and the publication of results. Have you ever noticed how a street railway or a bus company will count the passengers at certain points, day after day, before making a change in the route; or how a hydraulic engineer will measure the rate of flow of a stream at every month in the year before developing his plans for harnessing it? But these are studies which involve nothing but the expenditure of money, whereas we are dealing with human lives. How much more important, therefore, that we should test our ideas thoroughly before trying them on our patients or committing them to print.

Membership in this Association is a wonderful thing. I remember the thrill of delight with which I read the telegrams of congratulation that came in one Saturday afternoon after my election. I recall, too, the wonderful stimulation I have received from my unbroken attendance at its meetings for the past 26 years. Nothing that could have happened to me could have helped me more on the rough road of a surgical career.

The recollection of these early years stirs me to repeat what several of my predecessors in this chair have said, namely, that in selecting our new members each year we should choose young men who have a large part of their productive career ahead of them and who give promise of being able to take part in our discussions in a constructive way; men who as a result of close association with the distinguished members of our Society may develop even more fully than they could otherwise have done. It seems to me that we should reserve the election of men who are close to or past the retiring age—to a very distinguished few—no matter how distinguished they may be.

Our membership, indeed, is divided according to age into three broad groups. First and most important are the young, upon whom we must depend for the advancement of our art and science. Then come the middle aged who represent success and who are in command of our educational programme. To them let me recall the demand of our people from the Atlantic to the Pacific and from Hudson's Bay to the Rio Grande for first class surgical care. To provide it we must turn out hundreds of well qualified men every year. This means that every medical school and every first class hospital must join together in providing our young graduates with the necessary years of supervised internship and residency and with well planned postgraduate courses in anatomy, physiology, biochemistry, and surgery. Unless we present our candidates properly trained our Board of Surgery and our Colleges of Surgeons, because of the standards they are setting, will defeat rather than help in providing for the surgical care of our people. I suggest that for the next 20 or 30 years the chief duty of the members of this Association is to give leadership and guidance in this great program of Graduate Training in Surgery.

And finally, there is among our membership a smaller group who once belonged to the other two but who, because of the lapse of time are now senior members. I note with sadness that there are only ten men here today who were present at my first meeting and that there are only 25 members left of the 200 who were members then. The loss this year of our beloved President, Elliott Cutler, of our distinguished Honorary Member, Sir John Fraser, the Principal of Edinburgh University, and of my close friends John McCreary, Roscoe Graham, and Fraser Gurd and William Darrach brings thoughts that are sad indeed. On behalf of those who are in the senior group, however, let me assure you that we shall be coming to these meetings as long as we can walk. We want to see and hear the new members, to mingle with the young men who we hope will carry the traditions of the Society to even greater glories than in the past, and to renew our delightful associations with old friends. That you from time to time honour one of us by electing him to be your President brings great happiness to us all.

# STRICTURES OF THE COMMON DUCT\*

WARREN H. COLE, M.D., JOHN T. REYNOLDS, M.D.,

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CHICAGO, ILL.

ALTHOUGH THERE HAS BEEN GREAT IMPROVEMENT in the results following repair of strictures of the common duct during recent years, the outcome is far from that desired. Since the results are by no means perfect, and since such a large percentage of strictures are caused by operative trauma, meticulous attention must be paid to the technic of operations on the biliary tract in the prevention of these lesions.

## ETIOLOGY OF STRICTURES OF THE COMMON DUCT

In our series of 49 patients, operative trauma could be identified as the direct cause of the stricture in 65 per cent (Table I). In this group jaundice or a biliary fistula developed in one to three days following an operation on the biliary tract (usually cholecystectomy).

Numerous mechanisms in production of operative trauma are possible (Fig. 1). Perhaps the most common is excision of a mobile common duct which is placed under tension by traction on the gallbladder; the common duct is erroneously identified as part of the cystic and a portion excised. Another common mechanism is ligation of a portion or all of the duct with a bleeding vessel. It is possible that when considerable effort is made to ligate the cystic duct close to the common, the latter structure may be damaged. Occasionally, the duct is damaged during gastrectomy or traumatized sufficiently during choledochostomy to result in stricture formation; however, in our series none of the strictures could be attributed to either of these two causes.

In 11 patients, or 23 per cent of our series, an interval of three months to six years lapsed following the operation on the biliary tract before evidence of the stricture developed. The mechanism in production of these delayed strictures is poorly understood, but the authors agree with the original contention of Judd<sup>1</sup>, that a gradual obliterative cholangitis does occur and appears to be related primarily to inflammation. There are several possible causes of this inflammatory process in the wall of the common duct. The authors believe that a collection of bile overlying the common duct is a common cause of delayed formation of a stricture. A small abscess might produce a stenosis in the same manner. On other occasions neither of these two mechanisms appear to exert a role in production of the stricture. We

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\* Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

have had the same experience noted by Judd years ago, that a common duct observed at one operation was relatively normal in size, but at another operation several months later had stenosed down to a mere fibrous cord.

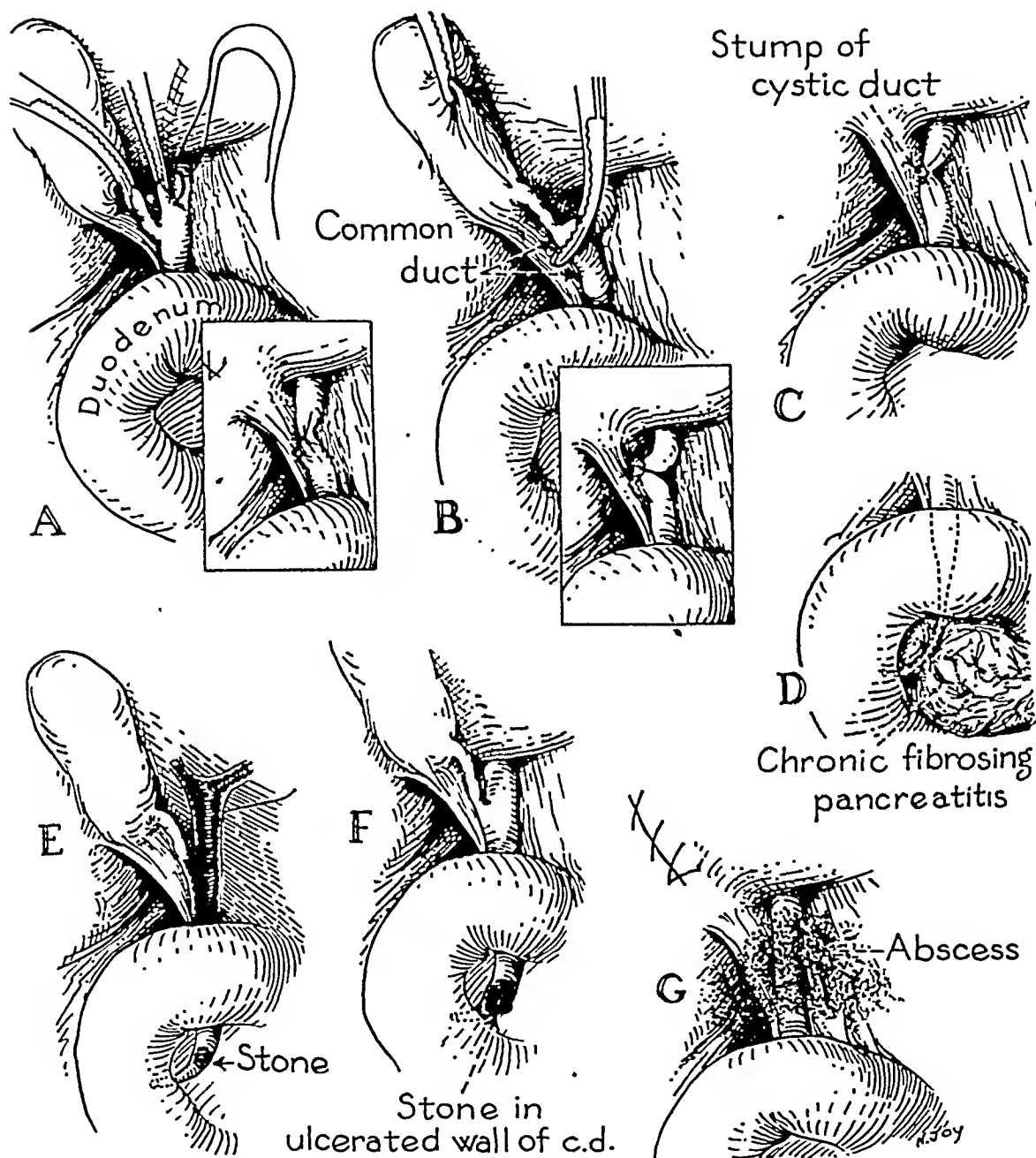


FIG. 1.—Mechanisms in production of stricture of the common duct; (A) transfixion with a needle; (B) ligation with the cystic duct; (C) ligation of the cystic duct too close to the common; (D) diffuse sclerosing pancreatitis; (E) cholangitis; (F) ulceration of the wall by stone; (G) abscess or local collection of bile. (From Cole, Ireneus and Reynolds, in *Strictures of the Common Duct*, Interscience Publishing Co., New York. In Press.)

Large masses of catgut and ligated tissue left adjacent to the common duct at the time of cholecystectomy might act as the source of an inflammatory process. On some occasions pylephlebitis appears to be the cause of the inflammatory stenosis. We have had four patients in our series of patients

with stricture who had pylephlebitis; it seems possible that this lesion may have been the primary etiologic factor in the production of stricture in these cases, primarily by contact infection.

In five patients, or 10 per cent of the series, the stricture was due to chronic pancreatitis of the diffuse fibrosing type. In two of these the obstruction was not complete.

Other factors such as pancreatic cysts, ulceration due to gall stones, etc., exist, but are relatively uncommon.

#### PREVENTION OF STRICTURES

Numerous measures can be utilized in operations on the biliary tract to prevent trauma to the common duct. If particular attention is paid to these

TABLE I.—*Causes of Benign Strictures of the Common Bile Duct  
(In Our Series of 49 Patients\*)*

	<i>No. of Cases</i>	<i>Per Cent</i>
1. Operative trauma (none following choledochostomy or gastrectomy)	32	65
2. Inflammation (some possibly related to trauma)	11	23
3. Chronic pancreatitis	5	10
4. Pancreatic cyst	1	2
Total	49	100

\* Only 4 patients (excluding the pancreatitis cases) were jaundiced before the original operation.

prophylactic measures the incidence of trauma will be diminished. Space does not permit detailed discussion of the measures, but they will be enumerated briefly below.

1. Maintain carefulness, and refrain from hurry while dissecting structures near the common duct.
2. Obtain good exposure of the region about the common duct with a long incision. The incision may be oblique, transverse or longitudinal, but should be of sufficient length to give adequate exposure.
3. Obtain adequate relaxation with the proper anesthetic. Ether is an adequate anesthetic in obtaining this relaxation, but cyclopropane and curare are likewise effective.
4. Isolate the junction of the common duct and the cystic duct before ligating the latter structure.
5. Ligate no artery until it is proven that it enters the gallbladder.
6. Ligate the cystic duct and artery separately.
7. Cut no structure until it is identified.
8. Ligate the cystic duct at least  $\frac{1}{2}$  inch from the common duct. This distance will protect the common duct and likewise prevent reformation of a bulbous tip.

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9. Control hemorrhage by pressure with the index finger of the left hand in the foramen of Winslow against the thumb, so the bleeding point can be controlled by compressing the hepatic artery. By gradual release of compression the bleeding point can be identified and caught accurately with an artery forcep.
10. If adhesions are dense around the common duct, start dissection at the fundus of the gallbladder and ligate the duct or ampulla high.
11. Eradicate gallbladder disease early before massive inflammation takes place.
12. Be familiar with the abnormal anatomy as well as the "normal". The anatomy of the biliary tract is so varied that we can identify no position of the various structures as normal. Normal can only be considered a composite of those types most commonly observed.

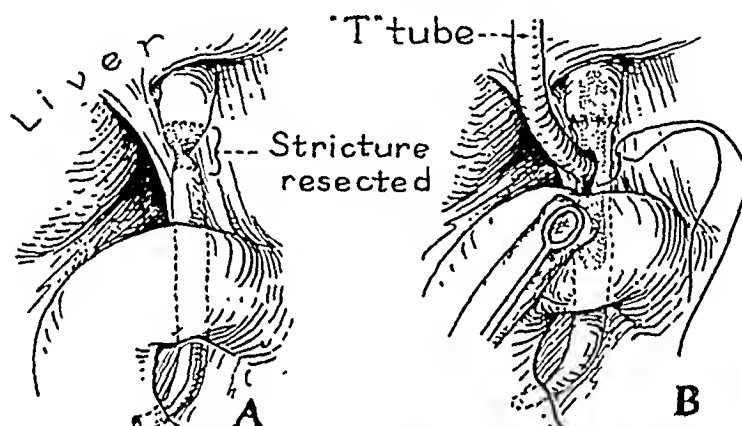


FIG. 2.—Repair of local stricture is best accomplished by resection of the stenosed area and end to end anastomosis. Support of the suture line is necessary for at least 3 months and is best accomplished by the arm of a T tube inserted through an opening  $\frac{1}{2}$  inch from the suture line. Every effort should be made to find the distal end of the common duct because the end to end type of repair, as illustrated above, is by far the most successful. (From Cole, Ireneus and Reynolds, in *Strictures of the Common Duct*, Interscience Publishing Co., New York. In press.)

### REPAIR OF STRICTURES

Since numerous types of stricture are encountered, numerous operative procedures must be available for the repair. It is now agreed by most surgeons spending considerable thought on repair of strictures of the common duct that the most difficult type to repair from the standpoint of recurrence, is the one occurring at the hilus of the liver. Unfortunately, when a stricture reforms, it is frequently at this point. Therefore, it is the opinion of the authors that the greatest improvement to be obtained in the repair of strictures would be in that group occurring at the hilus. Space does not permit a detailed discussion of the repair of the various types of strictures. Therefore, most of the text dealing with repair of stricture will be devoted to the details of a procedure which the authors have devised for treatment of strictures at the hilus. Other common procedures will be discussed briefly.

1. *Local Strictures*.—When a stricture is localized to a small portion of the common duct and does not involve the hilus of the liver, repair is easily performed by excising the scar at the stricture and performing an end-to-end anastomosis. One layer of sutures is adequate for end-to-end repair. Non-absorbable material is preferred but it must be placed carefully so that none projects into the lumen lest it act as a nidus for precipitation of cholesterol and bile salts. Some type of support must be furnished the suture line. The authors prefer a T-tube which is inserted through an opening at least  $\frac{1}{2}$  inch distal to the suture line, because insertion of the tube through the suture line tends to encourage recurrence of the stricture. (See Fig. 2.) A Penrose drain is inserted down to the duct as the wound is closed.

2. *Stricture of the Distal End Only*. — Several types of repair are available when the stricture involves the distal end of the common duct. The one preferred by the authors is a side-to-side anastomosis utilizing a longitudinal incision in the common duct as well as in the duodenum (Sanders<sup>2</sup>). In this anastomosis a double row of sutures is necessary; we prefer interrupted catgut for the inside row and interrupted silk for the outside row.

The common duct can be transplanted into the duodenum; however, the authors have not had very satisfactory results with this type of anastomosis.

When more than 2 or 3 centimeters of common duct are present, the authors are of the opinion that anastomosis of the duct to a functioning loop of intestine can be done without much danger of suppurative cholangitis resulting from reflux of food. There is apparently much less danger of cholangitis from reflux in this type of case than when no common duct is left, because the stump of common duct appears to act as a reservoir protecting the intrahepatic bile ducts.

3. *Stricture of the Proximal Portion of the Common Duct*.—In this type of lesion the repair becomes more difficult. If possible, effort should be made to find the distal end of the common duct, as emphasized by Cattell,<sup>3</sup> who actually splits the head of the pancreas in an effort to find it. If the distal end can be found, the duodenum and head of the pancreas can almost always be mobilized sufficiently to bring the distal end of the common duct up to meet the hilar duct, even though only a very short stump remains. In this situation, an end-to-end anastomosis is usually performed, as previously described, inserting a T-tube through an opening distal to the suture line so that the suture line may have support for as long as three or four months, thus minimizing the chance of recurrence.

4. *Absence of Entire Duct*. — This type of defect is the most difficult one of all to repair, and in general, results are not as good as in the lesions previously mentioned. The authors agree with Allen<sup>4</sup> and others that the use of a Roux Y arm of jejunum is superior to

anastomosis of the duct to a functional loop of intestine because reflux of intestinal content is so poorly tolerated by the liver when the stump of duct is so short that food regurgitates readily into the intrahepatic ducts. The authors proved to their own satisfaction that regurgitation of food could be a factor in production of chills and fevers, although stenosis is the more common factor. In two patients on whom we anastomosed a loop of jejunum to the hilar duct, the patients continued to have chills and fever which, however, were abolished completely several months later by section of the proximal arm of jejunum, thus preventing regurgitation. In bile duct repair, the credit for the use of the arm of jejunum designated as the Roux Y arm, should actually be given to Monprofit,<sup>5</sup> who recommended it in 1908.

*Use of Mucosal Graft from the End of Jejunum*—This procedure is a modification of one recommended several years ago by Hoag.<sup>6</sup> He suggested the use of a flap of gastric mucosa to be inserted up into the strictured area at the hilus of the liver. In view of the experiments of Price and Lee<sup>7</sup> showing that gastric secretions can actually digest, or seriously damage normal living tissue, we have modified this procedure by utilizing the end of the Roux Y arm of jejunum in the graft. This operation is designed primarily for strictures at the hilus of the liver, which is mentioned previously, as unquestionably the most difficult ones to repair from the standpoint of freedom from recurrence. After the Roux Y arm is constructed, the serosa and muscularis is separated from the mucosa and submucosa by sharp dissection for a distance of 2 or 3 cm., as illustrated in Fig. 3. This allows procurement of a tube of mucosa which can be inserted up into the strictured area, thus acting as a graft over the scarred area. After 2 or 3 cm. of mucosa are isolated, a portion of the bell end of a catheter (No. 10 to 14) is cut off and anchored with 2 or 3 sutures of interrupted silk or cotton in the lumen of the mucosal tube. It may be necessary to trim a portion of the mucosal tube, as illustrated in Figs. 3e and 3f. The cuff of mucosa is made long enough to extend through the scarred area in the liver up to normal mucosa of the bile duct, and is anchored in position by 2 silk sutures inserted from the outside into the depth of the duct opening, through the cuff of mucosa, and back through the interior of the opening to the exterior. When these sutures are pulled tight, the mucosal cuff is thrust snugly into the opening, thus producing a water tight closure or anastomosis.

At times considerable difficulty will be experienced in finding the dilated duct at the hilus of the liver. On several occasions we have been unable to find any external duct, but have encountered the duct by aspiration, as illustrated in Figure 3a. An opening is made into the duct by incising alongside the needle with a sharp bistoury. This opening is enlarged by blunt or sharp dissection, making effort to locate any adjacent vessels by aspirating around the opening with a hypodermic needle and



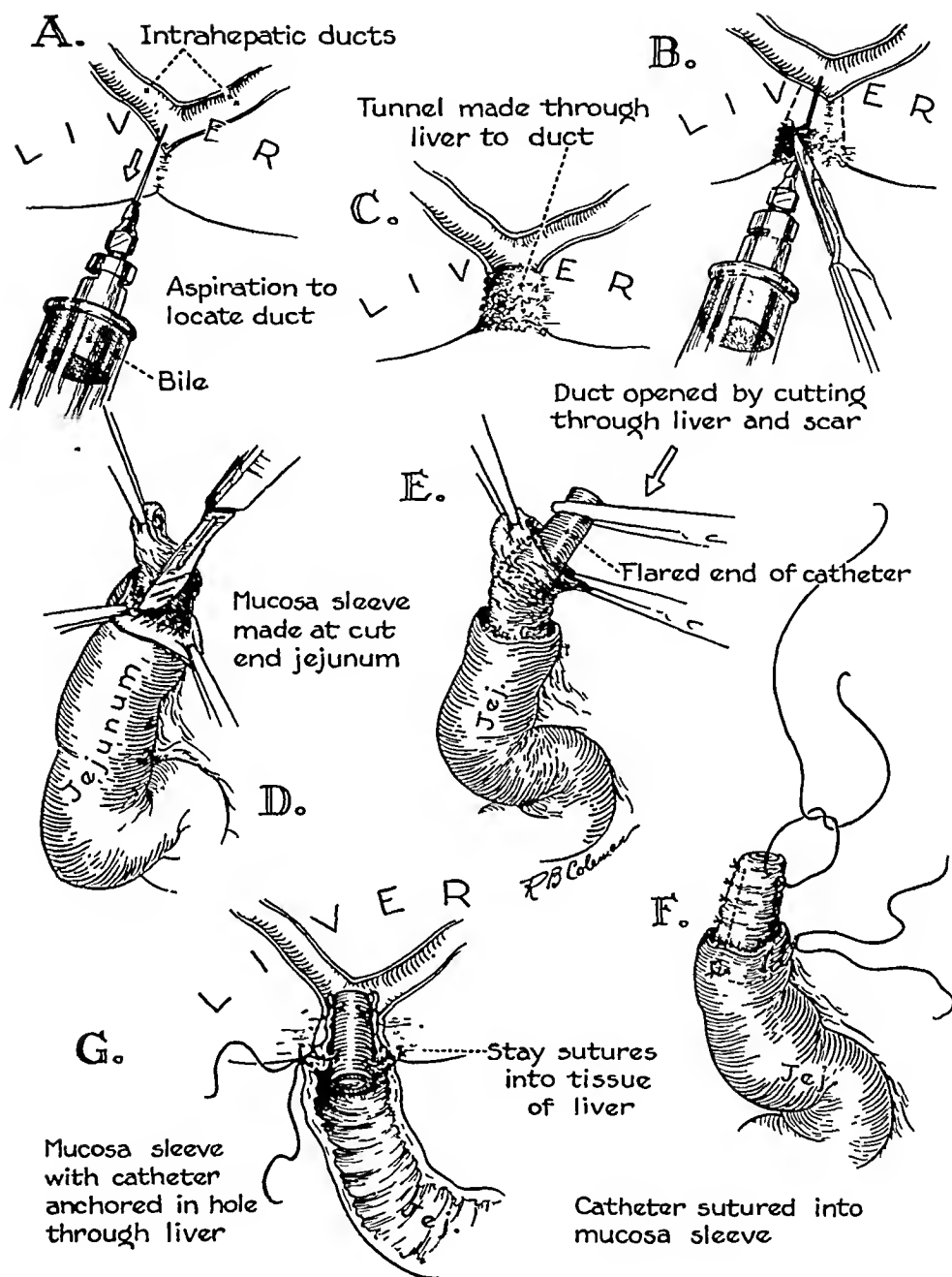


FIG. 3.—Repair of stricture of common duct by preparation of a mucosal tube and the implantation as a graft into the duct opening at the hilus of the liver (modification of Hoag operation). This procedure is most applicable when no stump of duct remains, and scarred liver tissue must be incised to reach the duct. The depth of the scarred area is exaggerated to better illustrate the method. The mucosal tube is pulled into position and held there by two sutures, each of which is inserted from the outside into the depth of the opening, through the mucosal sleeve, and back through the depth of the opening to the outside where the two ends of each suture are tied together. From Cole, in Canadian Med. Assoc. Journ. In press.)

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syringe. The opening so obtained usually extends through scarred liver tissue. In our opinion about the only hope of preventing reformation of a stricture at this point is to fill in the defect with a bridge or graft of mucosa. It would no doubt be satisfactory to insert the entire end of jejunum into the opening, but the opening is usually so small that one can get no more than the thin cuff of mucosa, as described above, in the

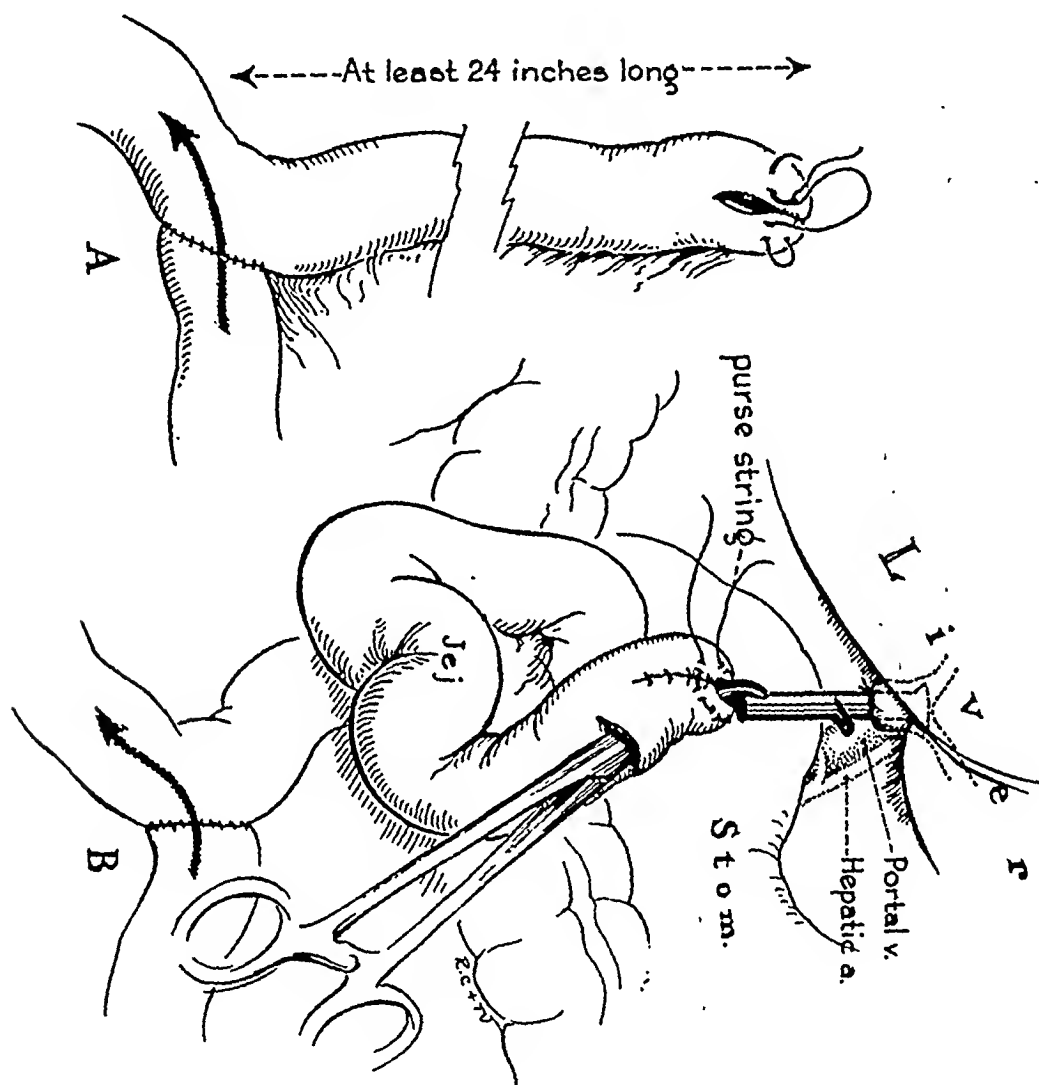


Fig. 4.—When utilizing the Roux Y arm of jejunum to replace the common duct, the ileum is severed about 18 inches from the ligament of Treitz and the proximal end sutured to the distal loop at least 14 inches from the point of severance; the distal end is closed with a continuous suture as shown in A. The end of the vitallium tube is inserted into the end of the intestine, aided by a hemostat through a puncture wound two or three inches from the closed end as shown in B. The end of the Roux Y arm of jejunum is anchored to the liver by interrupted silk sutures. (Modified from Cole, Ireneus and Reynolds, in *Annals of Surgery*, 1945.)

hole and still have room for an adequate lumen. Since this opening at the hilus is usually funnel shaped, even compression is best obtained by utilizing the flared end of the catheter, placing the smaller end upward into the opening. The wall of the jejunum is anchored in position against the hilus of the liver with three or four interrupted sutures of silk or cotton. In our experience the sutures anchoring the tube in the sleeve

of jejunal mucosa will tear out in three or four months, thus allowing the rubber tube to pass.

*Use of Vitallium Tube.*—The technic using a vitallium tube in the method of repair utilizing the Roux Y arm of jejunum has been described previously by the authors.<sup>8</sup> The important features in this procedure

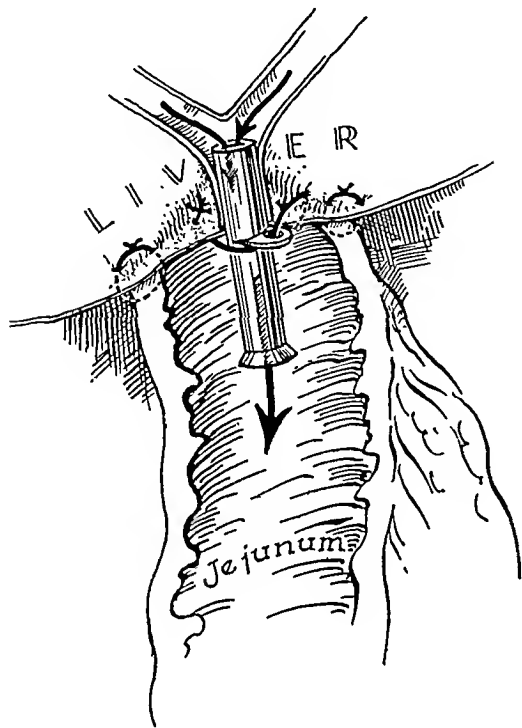


Fig. 5.—An alternate method of suturing the end of the Roux Y arm of jejunum to the hiliar duct when the duct protrudes at the hilus is to suture the end of jejunum as near the duct as possible with 4 interrupted silk sutures, without everting or infolding the edge of intestine. In the author's opinion, this type of attachment may minimize recurrence of stricture slightly more than the method illustrated in Fig. 4, although a true mucosa to mucosa anastomosis is not possible with either method. Mucosa to mucosa approximation is possible with the method illustrated in Fig. 3, and in the method shown in the above illustration if a wedge of the end of intestine is resected as shown by the dotted line through the mucosa of Fig. 3E; the edges on the side of the intestine are then turned in to prevent leakage. The mucosa of the conical shaped end of jejunum thus formed can then be anchored directly to the mucosa of the hiliar duct.

consist of anchorage of the vitallium tube (see Fig. 4) in the hiliar duct, turning in the end of jejunum, inserting the distal end of the vitallium tube into the arm of jejunum and suturing the end of jejunum to the hilus of the liver. Although we originally inverted the end of the arm of jejunum and anchored the vitallium tube with a purse-string suture, we are more inclined in recent cases, when utilizing the vitallium tube, to anastomose the cut edge of the arm of jejunum to the outside edge of the hiliar opening without inversion of the end or formation of a cuff (Fig. 5). In the cases in which we have not anchored the vitallium tube with a purse-string around the neck of the tube we have adopted the principle of anchoring it against the wall of the hiliar opening with one silk suture through the flange, and another silk suture around the neck of the tube. Our experience with this type of suture in a few cases indicates that the tube remains in place about three months. In our opinion it is not entirely desirable to have the vitallium tube remain longer than six months because such a high percentage of tubes will block if they remain in position longer than this interval.

*Use of a Rubber Catheter.*—Use of a rubber catheter to support the suture line when anastomosing the hiliar duct to the Roux Y arm of jejunum has previously been described by Allen.<sup>4</sup> An opening is made

in the catheter to allow bile to drain through the upper end at the hilus downward into the jejunal arm and also to the exterior through the lumen of the catheter. Allen recommends that this catheter be left in place at least three months.

On a few occasions we have utilized a short piece of rubber tube to support the suture line, leaving it in position at the anastomosis but anchoring it in place with a silk suture leading out to the exterior (McArthur<sup>9</sup>). At the end of 3 or 4 months the anchoring suture is cut, thus allowing the rubber tube to pass on out into the intestine.

#### MISCELLANEOUS TYPES OF REPAIR

We have abandoned the anastomosis of the hilar duct to the duodenum primarily because our results were so poor that other procedures appeared more desirable. We are aware of the fact, however, that a few of our surgical friends are still using this procedure and apparently are having reasonably good results.

Several years ago, we anastomosed a loop of jejunum to the hilar duct in 5 patients, doing an enteroenterostomy between the arms of jejunum about 12 inches from the stoma at the hilus. We have had such poor results with this method that we have abandoned it. We were unable to prevent regurgitation of food up the ascending arm of jejunum into the liver even though a wide enteroenterostomy was performed between the two arms of jejunum. If ample time is taken by the roentgenologist in studying the barium flow in these cases, regurgitation into the intrahepatic ducts will be demonstrable unless folds or valves are made in the ascending arm, as described by us<sup>8</sup> a few years ago.

Although an anastomosis of the gallbladder to the duodenum or jejunum is a satisfactory operation in patients having inoperable carcinoma of the head of the pancreas, we believe the procedure is not advisable in benign lesions because of the regurgitation of food and intestinal secretions into the gallbladder. If an enteroenterostomy is performed, placing folds or valves in the ascending arm of jejunum will prevent regurgitation (Peterson and Cole<sup>10</sup>). If the patient has an inoperable carcinoma, these precautions are probably unnecessary since he will probably die of his carcinoma before the infection becomes serious.

#### RESULTS

Results of 63 operations performed in 49 patients by us in the past 10 years are summarized in Table II. In 28 patients upon whom we performed an operation suturing the Roux Y arm of jejunum to the hilar duct we had good to excellent results in 78 per cent. In 22 per cent of this group the operation was a failure. Vitallium tubes were used in about 75 per cent of patients having this type of operation. In 4 patients we used a modification of the Hoag procedure, utilizing the

mucosa at the end of the arm of jejunum to graft over the raw area of scarred liver as shown in Figure 3. Good to excellent results were obtained in 3, or 75 per cent of this group. In two of the patients, we were unable to find the dilated duct at the hilus, but encountered it 2 or 3 cm. from the hilus at a depth of  $1\frac{1}{2}$  inches from the liver surface. We made an opening alongside our needle spreading the opening by blunt dissection until we were able to insert the mucosal end of the jejunum as a mucosal graft. One patient progressed satisfactorily for 3 months but the stricture recurred shortly after this and she died a few weeks

TABLE II.—*Summary of Results in Repair of Strictures*  
(63 Operations in 49 Patients\*)

Type of Operation	No. Op.	Results** (Exc. of deaths)	Op. Deaths
Hilar duct to Roux Y (75% vitallium tubes)	28	78 good to exc. 22 failure	0
Hilar duct to mucosal flap jejunum (modified Hoag op.)	4	75% good to exc. 25% failure	0
Repair local stricture	7	86% good to exc. 14% failure	1
Hilar duct to duodenum	7	14% excellent 28% fair 58% failure	0
Miscellaneous types of operations	17	60% good to exc. 40% failure	3
Summary	63		4

OPERATIVE MORTALITY RATE 6%

\*Not counting one patient in whom no type of repair was possible because no duct could be found at the hilus.

\*\*In 3 cases less than 1 year has elapsed since repair. One of them is already listed as a failure; the results in the other two (good to excellent) cannot be considered permanent because of the short period since operation.

later. The other patient had recurring attacks of jaundice and chills for a few months, but for the past several months has had no difficulty except for an icteric tint in the sclera. The prognosis in conditions as described in these two patients would obviously be poor regardless as to what operative procedure was utilized. The series is too small to give us an index as to the value of the procedure, but at present we believe it offers the best chance of preventing recurrence when the stricture is located at the hilus.

In 7 patients we repaired a local stricture by excising the scarred area and doing an end-to-end anastomosis or a plastic repair of the Mikulicz type. One of these patients died about 10 days after operation. The remainder had good to excellent results.

On seven occasions we anastomosed the duodenum to the hilar duct. In

only one of these (14 per cent) was the result good or excellent. In 28 per cent results were listed as fair, and in 58 per cent were listed as failure.

In 17 patients we performed miscellaneous types of operations which in general yielded very poor results. Most of these operations were performed before we adopted the procedure utilizing the Roux Y arm of jejunum. In this group of miscellaneous types of repair, results were considered good to excellent in only 60 per cent.

In 1946 Pearse<sup>11</sup> summarized the results of numerous surgeons working in this field, and reported that results were considered good in 80.1 per cent of 106 patients in whom a vitallium tube had been implanted in a loop of jejunum for repair of stricture. He reported that in 79 patients the vitallium tube had been used to support a suture line attaching the hilar duct to the duodenum itself; in 42.8 per cent results were considered a failure. We concur in the conclusion that this procedure is undesirable and have used the vitallium tube to support the suture line between the hilar duct and duodenum in only one case. Pearse reported that recurrence of symptoms caused by blocking of the vitallium tube occurred in 11.3 per cent of his combined series.

In our series of 63 operations we had 4 deaths, representing a mortality rate of 6 per cent. Cattell reports an operative mortality rate of 13.8 per cent in 164 operations on 123 patients. Flickinger and Masson reported a mortality rate of 12 per cent in their series of 188 cases.

#### SUMMARY

In our series of 49 cases of stricture of the common duct we noted that operative trauma was a direct cause of the stricture in 65 per cent. As expected, the best results (86 per cent good to excellent) were obtained in local stricture which was repaired by end-to-end anastomosis. The next best results (78 per cent good to excellent) were obtained in the group having anastomosis of the hilar duct to a Roux Y arm of jejunum.

The most difficult type of stricture for repair is the one in which no duct whatsoever can be found, except at the hilus. In this type of stricture we are convinced that the use of the Roux Y arm of jejunum in bridging the gap represents the best type of operative repair. Although we have had fairly good results with the vitallium tube in supporting the stricture line in such cases, we have recently adopted a new technic, particularly when the stricture is located at the hilus. This method is a modification of the Hoag procedure. Instead of the mucosa of the stomach, we utilize the mucosa of the end of the Roux Y arm of jejunum to act as a graft in covering up the raw area of scarred liver at the hilus. This scarred area at the hilus (present when no stump of duct is found) represents the point where recurrence is most apt to take place. In our opinion, the recurrence rate will be high in those cases unless the area can be covered with a tissue which will minimize scar formation; covering the area with live mucosa of the jejunal arm should offer a better method of eliminating scar forma-

tion, although our series of patients with repair of this type is too small to allow conclusions as to results.

Extreme effort should be made to find the distal stump of common duct which allows end-to-end anastomosis in practically all cases, thus preserving the sphincteric action of the ampulla of Vater.

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DISCUSSION.—DR. ALFRED BLALOCK, Baltimore: Dr. Cole is to be congratulated on his excellent results in this type of difficult surgery. I arise to speak briefly of a method which Dr. William P. Longmire of Baltimore has developed in the laboratory, which has been used by him on several patients. Dr. Longmire would be the first to insist that this method should not be used except in those instances in which the more orthodox procedures, as described by Dr. Cole, have been attempted.

These patients usually have had repeated operations attempted. An incision is made which approaches the left lobe of the liver, thereby avoiding troublesome adhesions which are usually present on the right. Mattress sutures are placed in the left lobe of the liver and a wedge-shaped rather large piece of liver removed until one encounters a dilated duct which is seen at this point. A small area of liver surrounding the duct is removed. One may bring up a loop of jejunum and suture the mesenteric border of the jejunum to the lower edge of this denuded liver segment. An opening is made in the jejunum and an anastomosis is made between this opening and the end of the dilated duct. This shows the completed procedure with the jejunum sutured to the liver.

The first such operation was performed by Dr. Longmire about 14 months ago on a patient who had a traumatic stricture of the common duct. Previous operation had been attempted on several occasions. There had been considerable elevation of serum bilirubin and this fell during the postoperative period, not entirely to normal but it approximated normal. The jaundice disappeared.

Dr. Longmire has used this procedure on three patients to date and the results are encouraging. In a patient operated upon last week the dilated duct on the left was really tremendous—at least a centimeter in diameter—and a very good anastomosis was performed. He has attempted it on several patients who have congenital atresia of the bile ducts, but in cases thus far he has not found a suitable dilated duct.

DR. FRANK H. LAHEY, Boston: I think it is well worth while, even though we have all discussed strictures of the bile duct again and again, to go over the subject again and again because everyone's results with this condition are far from satisfactory. I do not care what method you use to reconstruct injuries to the bile duct, they are in general makeshift procedures. A great many of them do not work or work only for a time and have to be done over. It makes no difference what type of tube you put in; if there is a defect in the duct and you do not get the ends together, most of them will eventually plug, require removal and the insertion of another tube. These operations are trying and tedious, and one does not have the gratifying reward that so often goes with other types of trying and tedious surgical procedures. Many of these patients eventually become jaundiced and get into trouble again.

For these reasons it is, I believe, valuable to discuss the various methods and, as in previous discussions, we wish again to speak of one which has given us the best results of all types of repair of these ducts. In any repair of an injured bile duct we have learned that one of the most important factors is the preservation of the sphincter of Oddi. Without the sphincter there will be a high percentage of cases that will have frequent ascending infection and undesirable jaundice and chills.

The other factor which we have learned in an experience now with more than 200 of these cases of duct repair, is that to get a satisfactory result one must have mucosa-to-mucosa anastomoses. We have learned that the introduction of tubes is a truly makeshift procedure and that while, as stated above, many of them will work, in spite of what has been said about them many will fail over a long period of time.

The principal method which Dr. Cattell and I have developed and discussed at various meetings is the demonstration and liberation of that portion of the common duct which runs through the head of the pancreas and is behind the duodenum where it is always protected from injury. We have learned from operations on the head of the pancreas and from dealing with many duodenal ulcers adherent to the common duct, that by rolling the duodenum to the left and splitting the head of the pancreas, a long section of uninjured common duct can be found. It is possible to so mobilize this that in many of the cases the freed lower end of the common duct can be brought up to where it can be approximated without tension to the lower end of the hepatic duct, and a direct mucosa-to-mucosa, end-to-end anastomosis can be done. In constructing these ducts it is necessary to support the anastomosed duct and to ensure patency of the tube while accurate healing is taking place. For this reason we have introduced a T-tube and left it in place for several months. It is important that this T-tube not be introduced through the suture line but either above or below, so that one arm passes through the anastomosis, and when it is withdrawn it leaves no defect in the suture line. This operation is not applicable to all cases, because many of the patients have been operated on several times and so much hepatic duct has been destroyed that a satisfactory upper end for anastomosis cannot be found. When it is applicable it is, in our opinion, the most useful and most dependable of all methods in terms of long-standing patency.



Another thing that we have learned about repair of injured ducts is that they should be attacked promptly. We used to wait until the patient had developed external sinuses, but we have now learned that the ideal time is while structures are still soft, pliable and movable, and that many times better results can be obtained then, than when, as a result of delay, cicatrization, fixation and distortion of the anatomy have occurred.

We would strongly urge that if repair is to be undertaken on injured ducts, that is, ducts that are known to be injured, it be done as soon as possible after operation. The operation is messy and oozy, and the structures are much more satisfactory to deal with at this time, but it will make possible better restoration of the ducts than will be possible at a later time.

As to the tubes themselves, I do not believe any interpretation of what the end results are will yield dependable figures unless they are observed carefully over a considerable period of time. Many of them drain satisfactorily for a year or two, only to plug eventually.

Personally, I do not like inflexible tubes such as vitallium. In my opinion they have no greater likelihood of maintaining patency than do rubber tubes and they have the great disadvantage of producing pressure and not adjusting themselves to the tortuous tracts into which they must often be inserted. No matter what type of tube we have used, many of them have had to be taken out and another tube inserted within three years because of their becoming plugged with bile salts.

It is, of course, trite to say that if one thinks only of the number of gallbladder operations done each year in the country, one realizes the exposure to the possibility of duct injuries and the very distressing surgical complications which go with them. It is so rightly said by everyone discussing this subject that the best approach to it is to teach that surgery of the biliary tract is dangerous surgery and must be done with good exposure, under good light and with accurate anatomic demonstration of every detail.

DR. HERMAN E. PEARSE, Rochester, N. Y.: I think it is interesting to note that Elliott, in a presentation before this Association found 26 per cent successful results. Now, though we have different methods and personal preferences our score has risen to approximately 80 per cent. That is worthy of comment. I am inclined to agree with Dr. Lahey that the best way to repair the damage is by direct end-to-end anastomosis. If one can reconstitute the patient's anatomy the way God made him, one will have better physiologic function. However, I have no quarrel with the Roux type of procedure and use it when necessary.

Contrary to the opinion of some, I have no stock in vitallium. I have tested out most of the available materials and have found that vitallium is the best for this purpose. It has faults and so I am searching for a better material.

The final point is that in the Roux type of biliary anastomosis, for which we should give credit to Allen Whipple for popularizing, the best length of the anti-peristaltic loop has never been accurately determined. Dennis used a 24-inch loop. I was inclined to use a 10- or 12-inch loop. These patients were studied under the fluoroscope and it was found that the barium would reflux up that loop approximately six inches. In spite of this, some develop cholangitis with a ten-inch loop. Recently, in conjunction with Dr. Radakovich, we have found in dogs that the minimum length for protection is 12 inches.

DR. WARREN H. COLE, Chicago (closing): I wish to thank the discussants for their valuable contribution to this subject today. I believe the method presented by Dr. Blalock and Dr. Longmire has splendid possibilities and should be tried when the duct cannot be found at the hilus. About a year ago I tried a modification of their

procedure on an infant with congenital artresia of the bile duct, but even though I amputated the entire left lobe I could not find a dilated duct to use in any sort of anastomosis.

Dr. Lahey has emphasized the importance of obtaining a mucosa-to-mucosa approximation whenever possible. However, on certain occasions a true anastomosis of this type cannot be accomplished.

In closing, I wish to emphasize that we should find the distal end of the common duct if at all possible, because the sphincter of Oddi is an important structure which the surgeon cannot duplicate.

# THE QUANTITATIVE AND QUALITATIVE CONTROL OF BILE FLOW AND ITS RELATION TO BILIARY TRACT SURGERY\*

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CHOLECYSTECTOMY WILL GIVE satisfactory results in 80 to 90 per cent of the cases where stones are present provided adequate effort is first made to establish a correct diagnosis of gallbladder disease. When cholelithiasis is not a part of the pathologic picture, satisfactory results approximate 60 per cent. In this latter group without stones, the error probably occurs because of a greater incidence of the nervous element, incorrect diagnosis and additional gastrointestinal disturbances, while in the former group, remaining common duct stones or debris are the most common causes for unsatisfactory results. Certainly spastic or atonic conditions of the choledochal sphincter play a role in the post-cholecystectomy syndrome and these conditions may be associated with bile stasis and infection.

The elusive remaining common duct stone is known to every surgeon. No doubt many stones which are found in the common duct at a secondary operation were present in the common duct at the time of the first operation. Nevertheless, the surgeon has an escape when it is appreciated that 7 per cent of all cases of cholelithiasis have stones in the liver and these may be the source of the common duct stones removed at the second operation. This incidence of hepatolithiasis was reported by the writer<sup>3</sup> in 1944. Stricture of the common duct may interfere with bile flow through the common or hepatic ducts, particularly if the bile is quite viscous because of hepatic disturbances or if infection and inflammation are present along the bile ducts. It is my belief that following cholecystectomy or choledochostomy, not infrequently thick inspissated bile, collections of mucus, blood clots, debris and fine particles of precipitated cholesterol or calcium bilirubin are present in the common duct. No doubt many times these move out of the ductal system with return of normal bile flow, but likewise it has been proven by direct observation that such substances may remain in the common duct, and these may be the nucleus for development of common duct stones later on (Figs. 2 & 3). The conditions just reviewed are also factors to be seriously considered when reconstructive procedures are done to re-establish the flow of bile into the intestinal tract.

It is logical to assume that if we could qualitatively control bile flow we should be able to prevent development of biliary tract stones. However, regardless of the many interesting studies and researches on this problem, we have not been able to bring the development of such stones under control. However, we do believe that we are able to control bile qualitatively to the extent that we can produce a thin, watery bile which is less conducive to

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stone formation along the ductal system after cholecystectomy, and can provide a type of bile that flows more readily through the ductal system, particularly if some narrowing of the channel exists. By controlling the quantity of bile, we are able to accelerate its flow and increase intraductal pressure to bring about a flushing out effect.

In discussing bile physiology and chemistry, one must frequently refer to the many studies and publications of Ivy <sup>1, 2, 10, 11</sup> and those who have been associated with him. My own interests have been directed toward the production of a thin watery bile increasing intraductal pressure and promoting relaxation of the choledochal sphincter area in such a manner as to effect a flushing phenomenon of the ductal system. The excellent chemical and physiologic studies of bile by Ivy and his colleagues afford a foundation for any study referable to the quantitative or qualitative flow of bile. However, previous to the many studies by Ivy and his group, Neubauer <sup>12, 13</sup> in 1922 and Pohl <sup>16</sup> in 1922 had started investigations on the pharmacological action and therapeutic uses of chemically pure bile acid. Since then many papers have been published on the pharmacodynamic action of various bile acids and bile salts.

Ox bile and pig bile have been used empirically as therapeutic measures for many years. Later investigations proved that ox bile more closely resembles human bile as cholic acid is predominant in both human and ox bile. The essential bile acid in pig bile is hyodesoxycholic acid. Other bile acids are also present in bile and the toxicity of these various acids have been studied by several methods. It was found that by oxidizing cholic acid triketocholanic acid (dehydrocholic acid) was produced. Pure dehydrocholic acid has been proven to be the least toxic of all. The type of bile produced in man and animal by giving oxidized bile acids orally or intravenously is different from that produced by using ox bile.

The salts or acids of glycine and taurine are natural constituents of bile and when bile acid exists in conjunction with glycine or taurine, the term conjugated is applied. The chemically pure bile acids do not contain glycine or taurine.

For the sake of clarity, the various bile preparations most commonly used should be described briefly.

Ox bile is an unoxidized conjugated preparation containing unoxidized cholic acids and some other bile acids in conjugation with glycine and taurine. Oxidation while retaining the conjugation with glycine and taurine results in the oxidized conjugated preparation available under the trade name dechacid. When the glycine and taurine are dropped in the oxidized preparation, an oxidized unconjugated product is formed, consisting of triketocholanic acid (dehydrocholic acid) and di and mono ketocholanic acids. This product goes under the trade name of ketochol. The pure triketocholanic or dehydrocholic acid goes under the trade name of decholin or procholol.

It is possible that with more thorough knowledge and clearer understanding of these substances as they qualitatively and quantitatively affect the bile, we will be able to improve surgical results in biliary tract surgery. This may be accomplished by anticipating certain complications which threaten some operative procedures or correcting complications which have developed by the proper application of our knowledge of bile acid or salt therapy.

Berman with Ivy and colleagues,<sup>1, 2</sup> reported in 1940 on a large group of experiments where various bile acids were fed to dogs with biliary fistulae. The bile volume, water, specific gravity, viscosity, total solids, bile acids (cholates), cholesterol, bile pigment and natural bile salt amounts were studied. Others have also conducted experiments on various phases of this investigation. These studies are consolidated in Tables I and III.

TABLE I.—*Summary of Changes in Bile*  
(Berman, Ivy, Doubilet, Best)

	Ox-Bile Salts(1)	Dechacid(2)	Ketochol(3)	Decholin(4)
Bile Volume .....	+	+	++	+++
Water .....	— per/cc.	No change	+	+
Sp. Gravity .....	No change	No change	per/cc.	per/cc.
Viscosity .....	+	No change	No change	No change
Total Solids/cc. ....	+	No change	—	—
Bile Acids—Conc. ....	+	No change	—	—
Cholesterol .....	+	+	+	—
Bile Pigment .....	No change	No change	No change	No change
Natural Bile Salts .....	+	No change	No change	No change
Result .....	Thick bile	Average	Thin bile +	Thin bile + +

- (1) Ox-Bile Salts — unoxidized conjugated bile acids (glyco & taurocholic)  
 (2) Dechacid — oxidized conjugated bile acids (glyco & taurocholic)  
 (3) Ketochol — oxidized unconjugated bile acids (tri, di & monoketocholanic)  
 (4) Decholin — oxidized unconjugated bile acids (pure triketocholanic)  
 Triketocholanic = dehydrocholic

TABLE II.—*Percentage Increase of Normal Bile Flow*  
(From Determinations of Berman et al)

	Volume cc. per 24 hours	Total solids per cc/24 hours
Ox-Bile Salts .....	+ 36%	+ 22%
Dechacid .....	+ 39%	+ 2%
Ketochol .....	+ 99%	— 8%
Decholin .....	+ 106%	— 22%
Ox-Bile Salts — Unoxidized conjugated bile acids (glycocholic & taurocholic)		
Dechacid — Oxidized conjugated bile acids (glycocholic & taurocholic)		
Ketochol — Oxidized unconjugated bile acids (tri, di & mono triketocholanic)		
Decholin — Oxidized unconjugated bile acids (pure triketocholanic)		
Triketocholanic acid = dehydrochloric acid		

Ox bile salts and dechacid increase bile flow and are choleric, while ketochol, decholin and procholol not only increase bile flow but produce a thin watery bile and are hydrocholeric.

It is noteworthy that ox bile salts, which contain glycocholic and taurocholic acid, increase the volume of bile but it is a type of bile with increased viscosity (Tables I, II, IV, V). There is a relative decrease of water per cubic centimeter and an increase of total solids and natural bile salts. Although cholesterol and bile acids are increased, there is no change in the cholesterol-cholic acid ratio so there is probably no increased tendency for cholesterol precipitating and becoming the nucleus for a stone. Likewise,

there is no decreased tendency. No change in the specific gravity or bile pigment values occurred with the use of either the choleretics or hydrocholeretics. The viscosity of the bile produced by these various bile products was measured by the time of flow between two points in a long slender glass tube (Table IV, V). Bile affected by prescribing ox bile is more viscous than normal bile, flows more slowly, and has more difficulty in making an exit through narrow channels. The volume increase as measured by cubic centimeters for 24 hour periods reveals a 36 per cent step up of bile flow (Table II). The total solids per cc. for each 24 hours is increased by only 22 per cent but the viscosity determination reveals the bile to be thicker than normal.

The product dechacid is also conjugated, containing glycine and taurine, but it is oxidized. It is a choleretic as it increased bile volume, but practically

TABLE III.—*Results of Oral Administration of Various Bile Acids in Biliary Fistulae in Dogs (Doubilet)*

Bile Acid Given	Volume of Bile	Total Bile Acids
Normal Excretion .....	150 cc.	3.37 Gm.
Pure Ox-Bile Salts .....	265 cc.	8.18 Gm.
Dehydrocholic Acid .....	510 cc.	4.75 Gm.

TABLE IV.—*Viscosity Determination (Berman et al)*

Time of flow between two points on a long slender glass tube

	Average Time
Distilled water .....	1 min. 30 sec.
Control bile .....	4 min. 15 sec.
Ox-Bile bile .....	4 min. 50 sec.
Dechacid bile .....	4 min. 30 sec.
Ketochol bile .....	3 min. 40 sec.
Decholin bile .....	3 min. 20 sec.

no other change occurred except a slight increase of cholesterol content which may or may not be of significance. The ultimate result is an increased volume of average type bile.

Ketochol, an oxidized preparation not conjugated with glycine or taurine, effects a larger bile volume than the above products. The water content is increased, total solids are decreased, and it is believed that in general bile acids are decreased. The cholesterol content is increased. There is no relative change in the specific gravity, bile pigment or natural bile salt output, but the viscosity is decreased which results in a thin bile (Table II). Here we find a 99 per cent increase in bile volume, with a decrease in total solids of 8 per cent per cubic centimeter each 24 hours (Table III).

Pure dehydrocholic acid, represented by the products decholin and procholon, results in an increased volume of 106 per cent with a 22 per cent decrease in total solids per cubic centimeter in the 24-hour period (Tables II, III). Bile acid concentration is decreased, and these are the only preparations studied which resulted in a decrease of cholesterol output (Table I). There is no change in specific gravity, bile pigment or natural bile salt

determinations. The viscosity determination is the lowest for this group of cholericics and hydrocholericics (Tables IV, V).

Doubilet<sup>9</sup> studied the results of oral administration of various bile acids in biliary fistulae in dogs (Table II). It is noted that the normal excretion of 150 cc. per 24 hours increased to 265 cc. with the administration of pure ox bile salts and increased to 510 cc. with dehydrocholic acid. The total bile acids measured 3.37 Gm. for the normal excretion, increased to 8.18 Gm. with pure ox bile salts, and with dehydrocholic acid measured 4.74 Gm.

Our determinations for specific gravity did not reveal changes and with or without bile salt therapy this usually measured between 1009 to 1012. We then turned our attention to viscosity determinations, using long slender glass tubes and clocking the time of flow between two points. Distilled water, natural bile from T-tubes in patients, and bile from T-tubes in patients

TABLE V.—*Viscosity Determinations*  
(Best)

Average Percentage Changes in Bile Flow Time

	% Increase	% Decrease
Distilled Water .....	Control	Control
Control Bile (Natural) .....	300% over water	
Ox-Bile Bile .....	10-15% over control bile	
Ketochol .....		15-20% less than control bile
		25-30% less than ox-bile bile
Decholin .....		20-25% less than control bile
		30-35% less than ox-bile bile
Procholon .....		Same as Decholin

TABLE VI.

Incidence of:	
Common and hepatic duct stones (Crump) .....	24 per cent
Liver stones (Best) .....	7 per cent
Choledochostomy (collected series) .....	9 per cent
Unsatisfactory results—cholecystectomy with stones .....	10-20 per cent

affected by administration of ox bile salts, ketochol, decholin and procholon were studied. We varied the diameter of the glass tubes and made comparative studies with tubes in varying positions (Table V). In these experiments, it took natural bile from T-tubes (control bile) about 3 to 4 times as long to traverse a given length of tube as it did distilled water. When ox bile was prescribed, the bile flow was 10 to 15 per cent slower than for control bile. It must be remembered that control bile from T-tubes varies as it is dependent upon a number of factors, including the liver status. In patients who received ketochol, the bile flow rate was 15 to 20 per cent faster than the control bile and 25 to 30 per cent faster than that of bile following administration of ox bile. With dehydrocholic acid products (decholin or procholon), the bile flow rate was 20 to 25 per cent faster than control bile and 30 to 35 per cent faster than bile following administration of ox bile. It is not difficult to conclude that the thin watery bile resulting from the administration of hydrocholericics passes more easily through the biliary ductal system, and the amount of bile being increased, it is conceivable that a relative washing or irrigating effect is obtained.

In 1939, the author with several colleagues<sup>4</sup> presented intraductal pressure studies showing that hydrocholeretics increased intraductal pressure by increasing bile flow. The ductal pressure varied with the resistance of the choledochal sphincter area, but in the individual case there was a definite relative increase in the pressure as measured by a manometer under various circumstances. When the hydrocholeretic products were given by mouth, the pressure was increased and sustained for hours or days. When given intravenously, there was a sudden and greater increase in pressure but this was not sustained (Fig. 1).

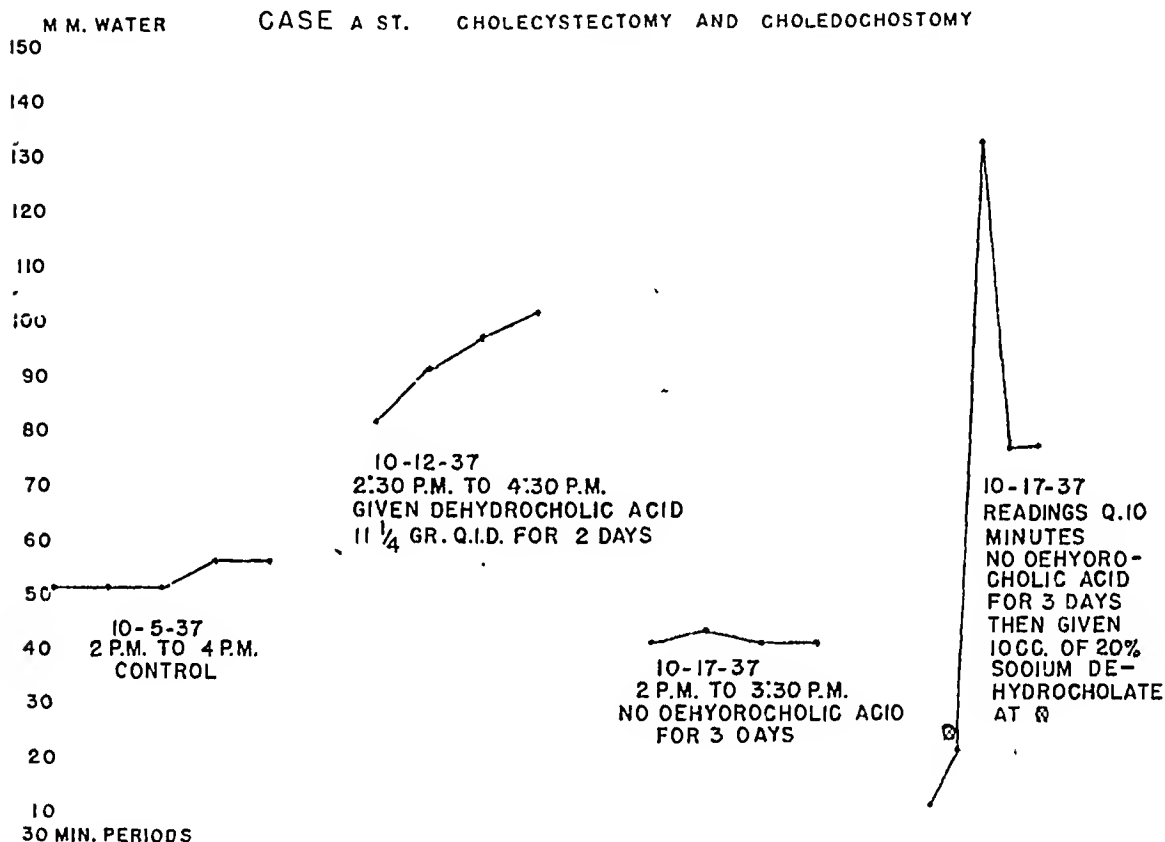


FIG. 1.—Intraductal pressure studies in a patient with a T-tube. Dehydrocholic acid orally results in an elevated sustained intraductal pressure. Sodium dehydrocholate intravenously results in a rapid increase of the intraductal pressure of short duration, but leveling off at a pressure slightly higher than the control pressure.

#### DISCUSSION

The greater percentage of unsatisfactory results in biliary tract surgery are due to remaining pathology or newly developed pathology in the common or hepatic ducts, most frequently stone or debris. A much smaller group of cases have had injury to the common or hepatic ducts and not infrequently the results of corrective or reconstructive procedures have not been satisfactory. Naturally, other causes exist but are relatively uncommon.

That remaining pathology in the common duct can be a very potent factor is exemplified by the fact that the number of patients with choleli-



thiasis who have stones in the common duct is much larger than the number of patients whose common ducts are explored. This is well illustrated by Crump (Table VI) who reported on his findings in 325 autopsies that revealed cholelithiasis. Of this group, 24 per cent had stones in the hepatic and common ducts, whereas analyses of hospital records rarely reveal that the common duct is opened and explored in one out of four cases of cholecystectomy for cholelithiasis.

One hundred hospital records in cases of cholelithiasis were reviewed several years ago. The surgery was performed by eight different surgeons and choledochostomy was done in only 9 per cent of the cases. My cases were not included because my own incidence of choledochostomy in cholecystectomy cases has varied between 20 and 44 per cent. If only 9 per cent of patients who have a cholecystectomy for cholelithiasis have intraductal exploration and autopsy studies reveal hepatic and common duct stones in 24 per cent of individuals with cholelithiasis, one can clearly reason that many of these patients must have remaining common duct stones. To further complicate the problem, my own investigations<sup>3</sup> prove that approximately 7 per cent of all cases of cholelithiasis have liver stones. Common duct stones are frequently elusive and escape detection in common duct exploration, only to be portrayed on the postoperative cholangiogram. Liver stones are a more serious problem because of their inaccessibility, and no doubt they may later reach the common duct and give rise to serious difficulty.

From our present knowledge of qualitative control of bile, we probably have little to offer in definitely and completely preventing precipitation or crystallization of substances within the hepatic or common ducts. However, an analysis of collected data (Table I) suggests that a hydrocholetetic consisting of pure dehydrocholic acid (decholin or procholone) not only decreases total solids per cubic centimeter and the viscosity of the bile but also decreases the cholesterol output. According to Berman, Ivy et al,<sup>1</sup> cholesterol does not accumulate in the blood. One could assume then that with less cholesterol available in the ductal system, there would be less opportunity for cholesterol precipitation which might subsequently serve as a nucleus or frame for stone development or collect as debris on rubber, vitallium or other substances used in corrective procedures on the common and hepatic ducts.

Pearse,<sup>14, 15</sup> who contributed the use of the vitallium tube in the management of some common duct lesions, presented before this society a year ago an excellent report on the results of the use of vitallium tubes. This was based on the experiences of a large number of other surgeons as well as his own. In three of his patients, when sediment had collected and blocked the vitallium tube necessitating its removal, he took advantage of the opportunity to analyze the sediment. The cholesterol content in the three cases was 38, 36 and 56 per cent, as compared to an average 70.6 per cent cholesterol level in the four thousand gallstones pulverized, mixed and analyzed by Dolkart<sup>8</sup> and his group. In the sediment analyzed by Pearse, the calcium

in the insoluble fraction varied between .0015 Gm. and .0075 Gm. and the remainder was bile pigment. In no case did bile pigment and calcium alone form the sediment blocking the tube. To me, this is an interesting contribution. If it is true, one is warranted in assuming that reduction of cholesterol content will at least be helpful in preventing sediment from collecting. Of course if the bile acid concentration also were decreased below the normal bile acid-cholesterol ratio, precipitation would probably occur but experiments do not reveal unfavorable disturbances in this ratio. Furthermore, if we decrease the viscosity, there is a more rapid flow of bile and precipitate or crystalline sediment is less likely to collect. This is especially true when the bile is a very thin, watery type flowing under increased pressure.

The choleretic, ox-bile salt, increases bile volume by 30 to 40 per cent, while hydrocholmetics increase bile volume 95 to 110 per cent. In corresponding dosages, the pure dehydrocholic acid (decholin and procholon) produces a slightly greater increase of bile flow than the mixture of triketocholanic acid (dehydrocholic acid) with di and mono ketocholanic acid (ketochol). This increased amount of bile flowing through the same size ductal system has a natural flushing or washing effect. There results a natural increased intraductal bile pressure but this may be varied by obstructing agents along the common or hepatic ducts and by the state of spasm or relaxation of the choledochal sphincter mechanism. We have studied the intraductal pressure in many patients with a T-tube in the common duct and have reported some of these studies. We have also studied the amount and type of bile in patients after prescribing cholergics and hydrocholmetics. Of course, many of these studies on the amount of bile flow were not too accurate because part of the bile passed on through the T-tube. However, in one case of complete biliary fistula resulting from common duct injury elsewhere, we catheterized the fistula and were able to collect most of the bile, and an attempt was made to make an accurate estimate of the small amount of bile on the dressings. In a number of other cases where stones almost completely blocked the lower end of the common duct, we believe we had fairly accurate readings on this increased bile flow in humans.

In 1938,<sup>5</sup> a report was made on the removal of remaining common duct stones by means of the biliary flush. We have made no attempt to report all of our successes or failures but in figures 4, 5 and 6, several cases are depicted. A definite regimen is followed, based upon the increased flow of a thin watery bile and the use of antispasmodic agents to relax the lower end of the common duct. Gradually we have collected further data by various studies and wider experience. During the last ten years we have made this flush a routine post-operative procedure in every case of biliary tract surgery. It has also proven particularly helpful in cases where the common duct has been repaired or reconstructed, with or without the use of rubber or vitallium tubes. Likewise it has been of great aid and has lessened our



FIG. 2.—Collection of debris or "muck" from a common duct. The smallest particle of cholesterol or calcium bilirubin, if remaining in the common duct, may be the nucleus of a larger obstructing or symptom-producing stone.

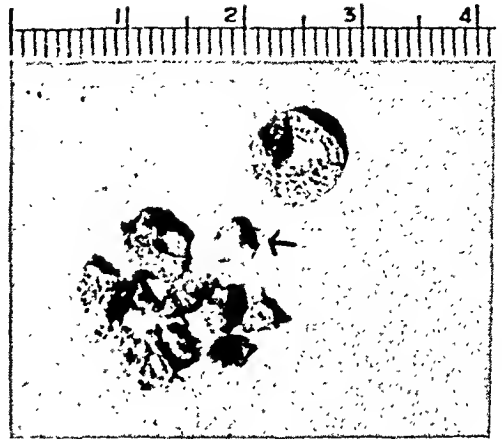


FIG. 3.—The arrow points to a small calcium bilirubin stone of the common duct which was the nucleus for a larger stone resulting in complete obstruction of the common duct. The bed of the small stone can be seen in the larger fragment.

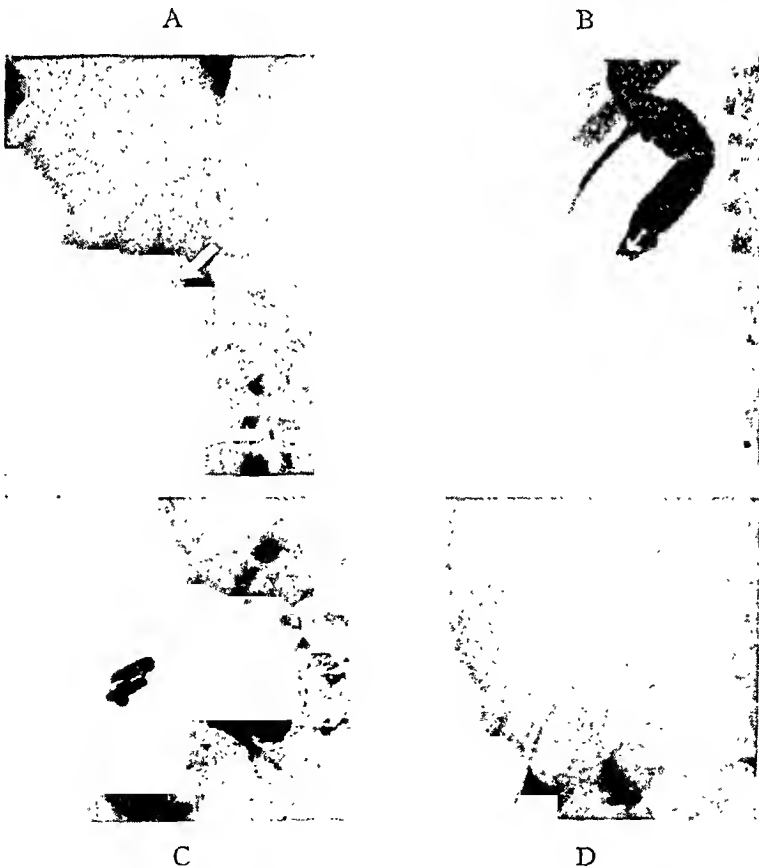


FIG. 4.—Stone could not be located when common duct was explored. Delayed cholangiogram (B) reveals stone at lower end of common duct. After four flushes and six ether-alcohol injections, stone was dislodged (C & D).

difficulties in cases where the hepatic or common duct has been anastomosed to the stomach, duodenum or jejunum with or without the use of rubber or vitallium tubes.

The following regimen is prescribed in all cholecystectomy cases:

1. Three decholin or procholon tablets after each meal and at bedtime for 3 days.
2. One teaspoonful of magnesium sulphate in water each morning.
3. Two tablespoonfuls of pure cream or olive oil before noon and evening meals and at bedtime.
4. On the first day, one nitroglycerin tablet (1/100 gr.) is placed under the tongue before each meal.
5. On the second day, one atropine tablet (1/100 gr.) is dissolved in a little water and taken before each meal.
6. On the third day, the nitroglycerin is repeated as on the first day.

In routine cholecystectomy cases, the flush is started on the seventh postoperative day and is repeated in two weeks. It removes the smaller crystalline or precipitate sediments which may be the nucleus of future stones, and other debris such as mucus, plugs, blood, and the so-called "muck" which we not infrequently see on exploring the common duct (Fig. 2). Also we have repeated evidence that single or multiple small to large stones are dislodged from the common duct.

In 1940, a critical analysis was made of 48 cases of cholecystectomy for cholelithiasis where there had been no indication to explore the common duct. All cases had been operated upon previous to 1936 and had not had the advantage of the biliary flush. Nine patients (18.7 per cent) continued to have symptoms, minor to severe, but definitely referable to the biliary tract. Six of these patients had their symptoms relieved by the biliary flush and two more found out by time and experience that it was necessary to take the flush once each month to avoid recurrence of some symptoms. One case was not relieved, and common duct exploration revealed a stone. Recently I have checked on 60 cases of cholecystectomy for cholelithiasis where there was no indication to explore the common duct and where at least one biliary flush and usually two had been prescribed postoperatively. All of these were operated upon at least one year ago, and a post-cholecystectomy syndrome was present in only four (6.6 per cent). In other words, cholecystectomy was satisfactory in only 82 per cent of the first group but in the latter group, with the aid of the biliary flush, results were satisfactory in 94 per cent of the cases. Three of the latter group are being kept comfortable by taking the biliary flush at monthly intervals. The fourth patient has had several attacks of colic and mild jaundice suggesting biliary dyssynergia or common duct stone. Some relief is obtained by the flush.

The flush regimen is used to dislodge stones in the common duct that are revealed by the routine postoperative cholangiogram (Fig. 4, 5, 6) which is always done in cases of choledochostomy. During the three days of the flush, the T-tube is kept clamped to permit building up of intraductal pres-

sure. Each day the tube is irrigated with warm olive oil after dissolving 1/100 gr. of nitroglycerin under the tongue. If the repeat cholangiogram reveals a stone still present, the same regimen is repeated a number of times. In addition, when necessary, various solvents or substances that will cause fragmentation or dissolution of the stone are injected into the duct. These

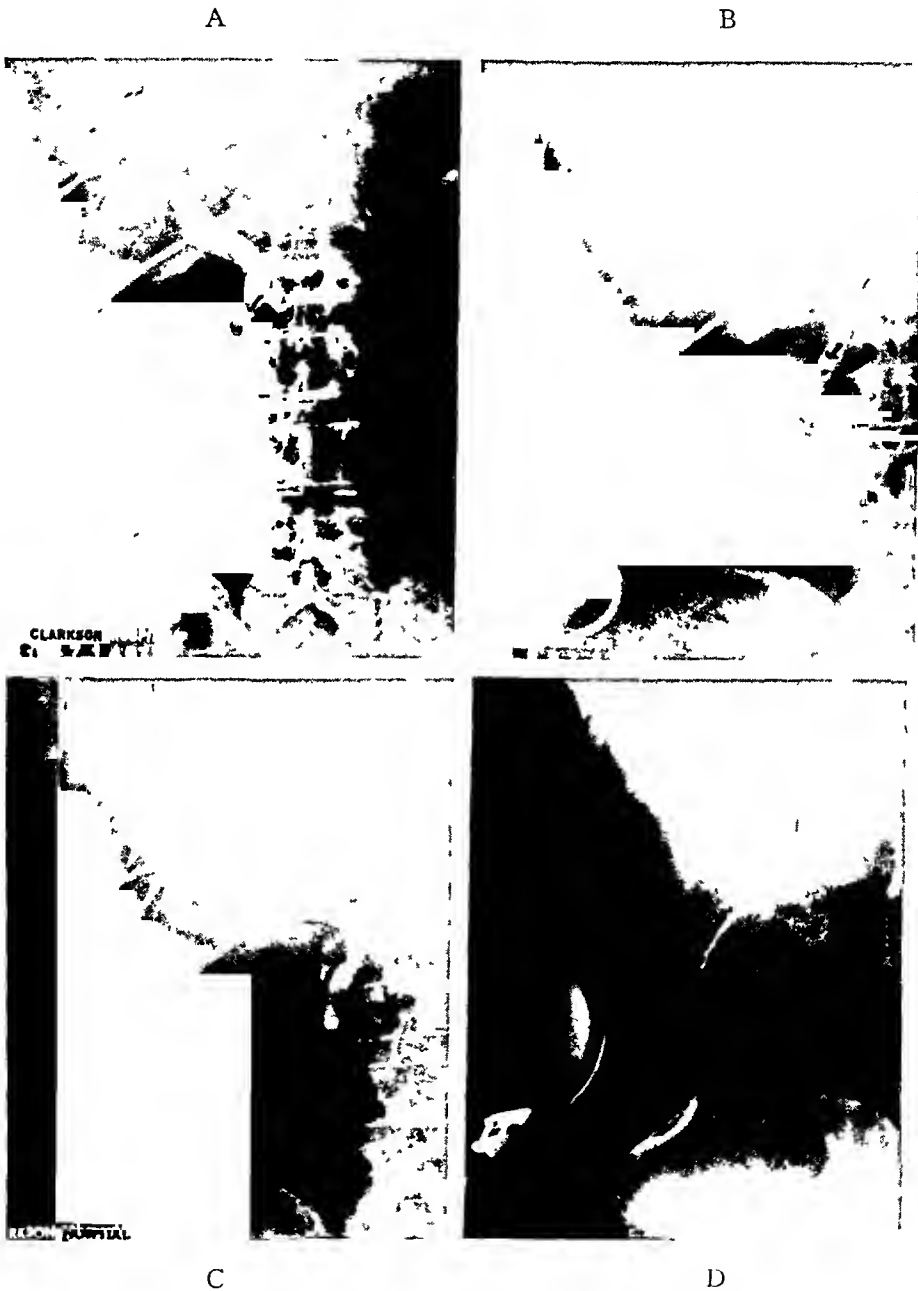


FIG 5.—This patient developed jaundice 26 years after cholecystectomy (elsewhere). We removed several stones from the common duct but delayed cholangiogram reveals a remaining common duct stone (A & B). After several flushes and ether-alcohol instillations, patient was sent home for several months. Upon her return, stone was still present but another flush with ether-alcohol instillation resulted in disappearance of the stone (C & D).



FIG. 6.—Cholecystectomy, with choledochostomy only because of small stones in the gallbladder but no stones found in the common duct. Delayed cholangiogram reveals a stone in common duct (A & B) After three flushes, and without ether-alcohol instillation, stone was dislodged from lower end of common duct (C & D).

include ether-alcohol mixture, chloroform and solution G, which have been previously described in detail.<sup>6</sup> We have had experience in handling our own patients as well as those of other surgeons, and have had reports on other patients whom we have not handled directly, and we believe that success attends about 30 to 40 per cent of the cases where these combined methods are used.

For more than eight years, we have directed every patient who has had a biliary-intestinal anastomosis, with or without the use of a rubber or vitallium tube, to take the biliary flush without the antispasmodic measures once or twice each month. This usually causes any ascending infection to subside and the beneficial effects have been well exemplified by improvement in patients who for some years had presented a serious problem because of chills and fever and frequent mild to moderately severe jaundice. A few patients have made an almost dramatic response, and others have been so much improved as to make the situation compatible with life. At times, the occasional use of the sodium dehydrocholate intravenously over a three day period has been necessary to obtain a beneficial effect. In most of these patients, and particularly where a rubber or vitallium tube has been used, we have recommended taking daily doses of the hydrocholeretic (two tablets night and morning) and taking the biliary flush without the anti-spasmodics once each month. Naturally, we have seen some patients whose improvement has been minimal.

In all cases of common or hepatic duct reconstruction, with or without the use of the vitallium or rubber tube, we place the patient on the complete three day biliary flush the first three days of each month and usually recommend that two tablets of the hydrocholeretic be taken night and morning during the remainder of the month. This regimen takes advantage of the flushing effect and in the interim a thin, watery bile is produced which has less tendency to develop a crystalline sediment or precipitate and flows more readily through any narrowed channel of the ductal system. We do not hesitate to say that in several cases where the vitallium tube had been used and rather serious symptoms developed, this regimen has changed the picture and re-operation has been avoided. It is strongly recommended that this regimen be instituted two weeks after surgery in every case where a vitallium tube has been placed in the common or hepatic duct.

As yet, we do not have complete and satisfactory experimental evidence that we can dislodge intrahepatic stones into the common duct. Theoretically it is a possibility and we have cholangiographic studies revealing stones in the upper hepatic duct becoming displaced into the common duct following the biliary flush. In some of our cases we prescribe the biliary flush previous to surgery.

We are of the opinion that in complete duct obstruction and jaundice, intraductal pressure should not be increased because of possible increased liver damage. There have been several experiments reported that are some-

what to the contrary. Nevertheless, we do not recommend it until some bile is appearing in the stools in cases where no fistula exists.

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DISCUSSION.—DR. HERMAN E. PEARSE, Rochester, N. Y.: I am very anxious to comment on the timeliness of this presentation. The clinical usefulness of the choleretics has been neglected. They are very important and, as our studies of the biliary physiology increase, I am sure that in the future we will have these and other substances that will help in clinical surgery. They are also useful in medicine, for as George Whipple pointed out a number of years ago, if pregnant women are given choleretics just before and after term, there is a great possibility of reducing the incidence of gallstones subsequent to pregnancy. They may also be used in the medical management of the non-calculus type of cholecystitis which, you will agree, is not a surgical disorder in its primary stages.



Choleretics may be used in the presence of occlusion of tubes placed within the bile ducts and in the amelioration of symptoms from such anastomoses as Dr. Cole presented. Such use may avert a failure. Studies on choleretics such as Dr. Best has presented may greatly simplify our management of biliary conditions.

DR. CHARLES G. JOHNSON, Detroit: For some years I have been interested in the study of the bile salt content of bile and its variations. I would like to ask Dr. Best, in relation to biliary flush, what he thinks of the possibility of utilizing it more or less continuously. I have found that if whole bile salts is given, the flow of bile is increased. This material has, in my hands, proved much better in alleviating post-cholecystectomy syndrome than any of the prepared or synthetic bile acids. If I give a patient whole bile and analyze the bile salt excreted through the common duct tube, or if this is done in the animal where one has better control, the first thing that happens is increase in the total amount of bile plus an enormous increase, amounting to practically a quantitative recovery of bile acid administered, if whole bile is given by mouth. Furthermore, if one analyzes the bile acid content of the total amount of bile excreted by the liver, one finds that bile acid is extremely well conserved and utilized. Bile acid will remain fairly high for a week after administration of whole bile. One need not give frequent doses of whole bile to keep the bile acid content of bile high with the associated cholorectic activity. Each time the increased bile comes down into the duodenum one gets additional cholorectic activity from it.

We have been too often in the habit of taking natural material, disintegrating it as much as possible, and selecting one part or another for use. The entire whole bile is preferred to extracted portions, and this can be obtained by addition of water to properly dried bile. It is pretty difficult to make bile, that is, to reconstitute bile from its components. I do not know anyone who has ever done it. Bile is an important material. It seems it makes no difference what type of bile one uses—from the pig or from the human or from the cow—despite the fact that bile salt concentrations, and the type of bile salts, are different in different species. The activity as measured by the sense of well-being of the patient, and the utilization of fat, seems to be just as good with one type of bile as with another.

DR. R. RUSSELL BEST, Omaha, Nebraska (closing): In answer to Dr. Johnston's question, we recommend that the patient have the 3-day biliary flush once each month and then take smaller doses of dehydrocholic acid (decholin or procholon) each day, i.e., one or two tablets only, night and morning. I do not agree that pig bile is as satisfactory as ox bile when whole bile products are indicated for increased flow of a normal or thick bile to aid digestive function. However, Dr. Johnston may have some knowledge on bile experiments that might nullify this statement. The work of Ivy and his associates makes me feel rather strongly at present that ox bile should be prescribed. A dehydrocholeretic product produces a sustained, increased flow of thin bile for at least some four to six days following oral administration. With bile salts the increased bile flow ceases rather early, as it is dependent more upon the amount of actual bile salts absorbed from the intestines. It is this absorbed bile that is excreted. In fact, I recall an experiment where the increase in bile flow was studied and the amount of bile salts (choleretics) administered orally was determined. This cannot be done with the prescribing of dehydrocholic acid products (hydrocholeretics).

I wish to express my appreciation to the discussants.

## SPLENECTOMY: WHEN IS IT INDICATED?\*

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The subject, when is splenectomy indicated, is automatically divided into three different aspects. The first is the surgical removal of the spleen for conditions directly related to the spleen itself, such as tumors, ptosis, rupture or cyst, to increase radicalness in total gastrectomy or to aid exposure in operations in the left upper quadrant. Secondly, there are those states which have to do with splenic effects upon the peripheral blood cells or upon the bone marrow and the production of red and white blood corpuscles as well as platelets. Finally, there is a third division in which the indications for splenectomy are less well established in terms of lasting benefit from it. This includes the early cases of congestive splenomegaly, and the patients in whom the splenomegaly is of unknown origin and for whom the question arises as to whether or not splenectomy would be valuable as a prophylactic against possible later splenic effects.

### GROUP I

The tumors of the spleen, such as lymphosarcoma and Hodgkin's disease that are rarely but occasionally limited, at least in the beginning, in their involvement to the spleen, require no discussion, particularly when it is realized, as will be discussed in a later section dealing with splenic effects on bone marrow and blood, that at any time true tumors of the spleen or infiltration of the spleen as a part of the disease known as Gaucher's disease or inflammation of the spleen can promote secondary bone marrow and blood cell effects, producing the blood condition known as hypersplenism. This secondary splenic effect, associated with tumors and inflammatory processes in the spleen, results in depression of blood platelets, depression of granulocytes and depression of red blood cells. If such splenomegaly results in this state, panhematocytopenia, there can be no reasonable disagreement regarding the wisdom of splenectomy.

We have had four true cysts of the spleen. Since these in no way are difficult to manage, it can be assumed that the indications for splenectomy in these states are likewise accepted by everyone, particularly when such cysts attain significant size.

The wandering spleen with which we have had but one experience, sub-

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\* Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

ject as it occasionally is, to torsion, likewise falls into the group for splenectomy, about which there would be no debate.

Trauma to the spleen, resulting in rupture and hemorrhage, likewise requires very little discussion. Located, as the spleen is, in the left upper quadrant and possessing, as it does, a definite pedicle also with quite inadequate fixation attachments to the posterior parietal wall of the abdomen, the spleen is subject to injury following any trauma to the left upper quadrant. This may occur even when an indirect force to the pedicle of the kidney results in transmitted effects on the splenic vein and artery as they pass from the tip of the pancreas into the hilum of the spleen.

There is little that need be said regarding the indications for splenectomy in rupture of the spleen except to recall that force or injury which results

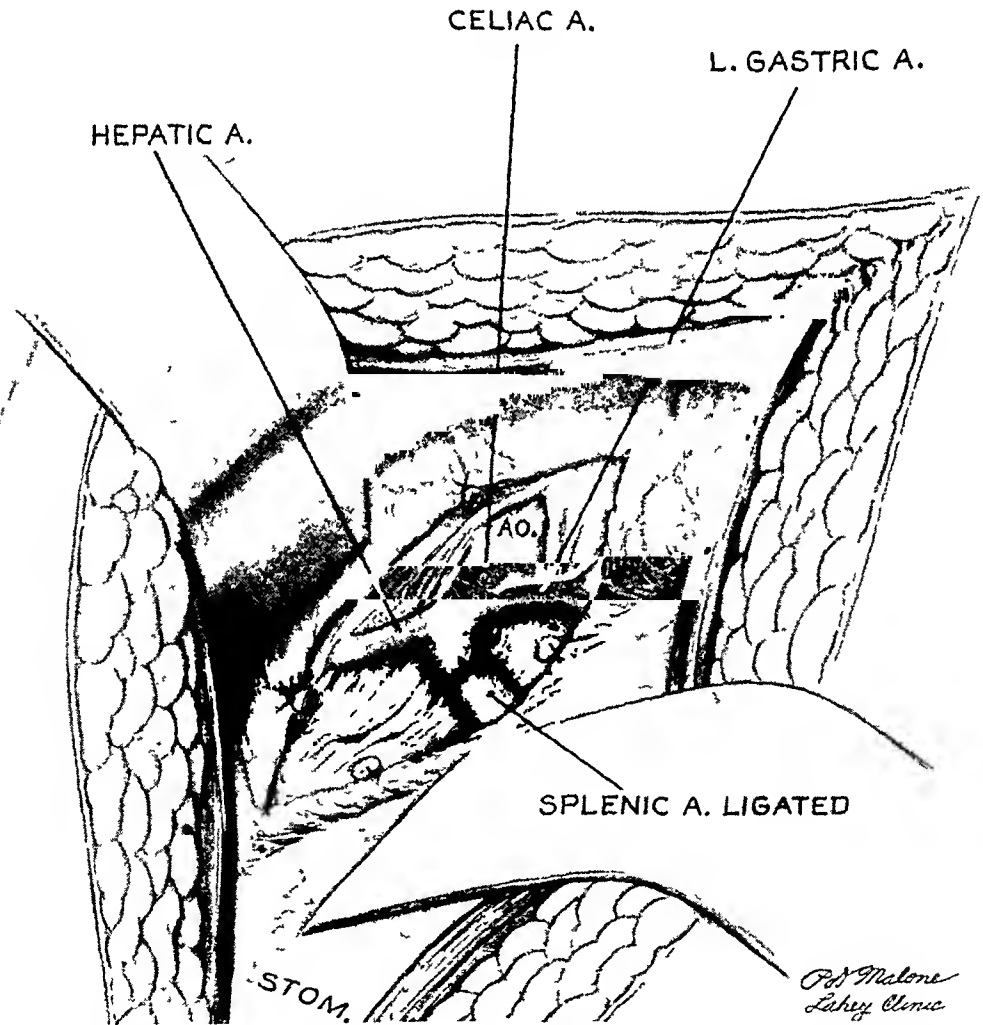


FIG. 1.—This illustration shows the preliminary ligation of the splenic artery close to its origin through the gastrohepatic omentum. This plan of controlling the arterial blood supply to the spleen close to the origin of the splenic artery is valuable, as discussed in the text in those large spleens difficult to displace and in those spleens, limited in number, with perisplenitis in which splenectomy is contemplated.

in rupture of the spleen is delivered also to the pedicle of the kidney. In splenectomies done for ruptured spleen one should always be sure that there is not present also an injury to the underlying kidney.

The type of splenectomy which is done upon ruptured spleen is quite different from the deliberate approach to the pedicle of the spleen when splenectomy is undertaken for splenic effects upon the bone marrow or upon peripheral blood cells as shown in Figure 2. Since the patient will be in a state of relative emergency, the less elegant but much more time-saving procedure of freeing the spleen from its peritoneal attachments by means of

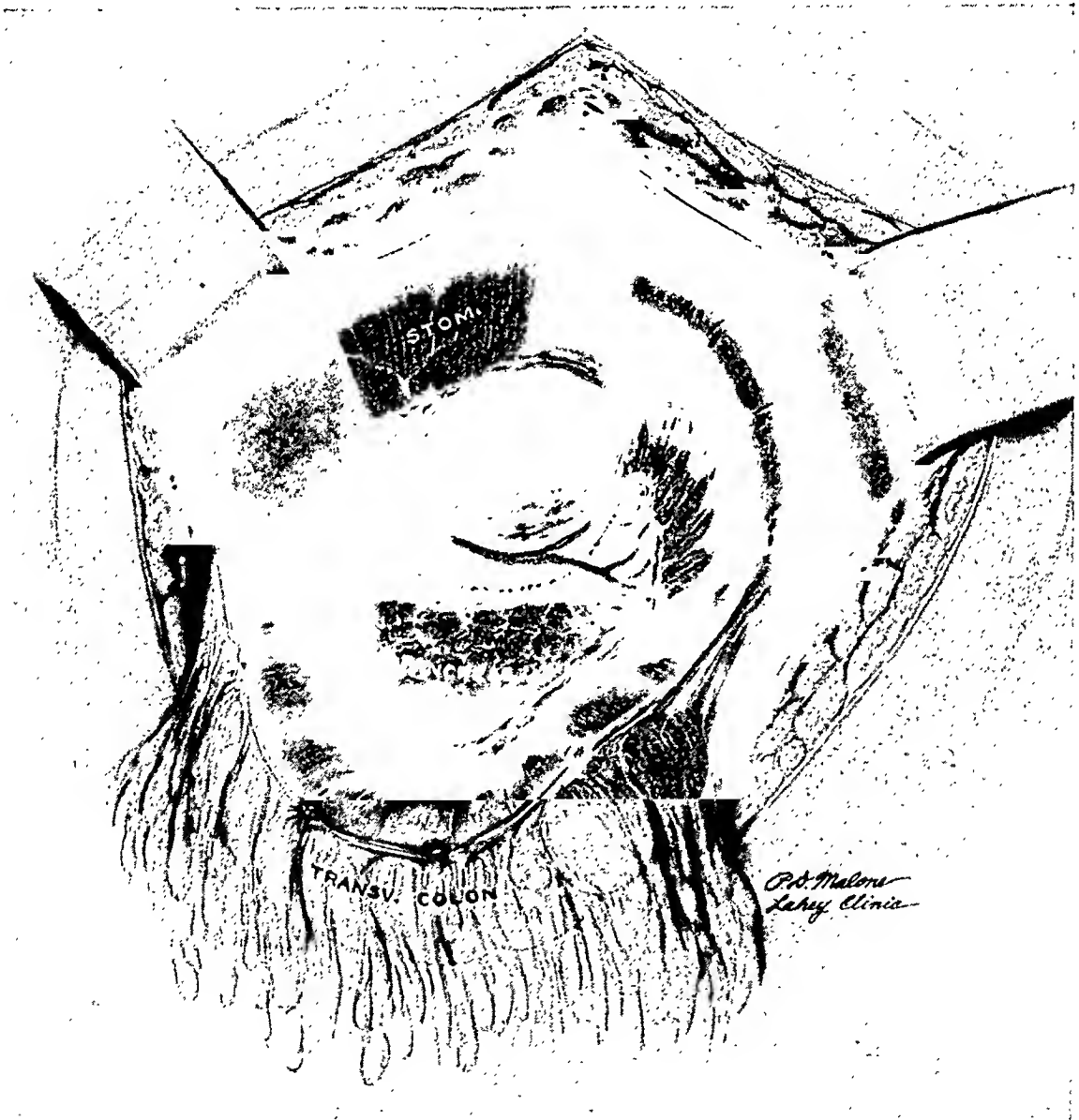


FIG. 2.—This illustration shows the most satisfactory approach to the vascular pedicle of the spleen by wide exposure through the gastrocolic omentum. As stated in the text, by means of this exposure, accurate control of the blood supply to the spleen is obtained and it is possible to make very adequate searches for accessory spleens.

This method of approach was described and illustrated by Dr. Albert O. Singleton, and undoubtedly is employed by many surgeons.

separating it bluntly with the finger, turning the entire spleen upward and inward together with the tail of the pancreas (Fig. 3) and ligating or clamping the splenic blood supply at once, will give immediate control of bleeding, lessen the amount of blood loss, and shorten the time required to do the operation.

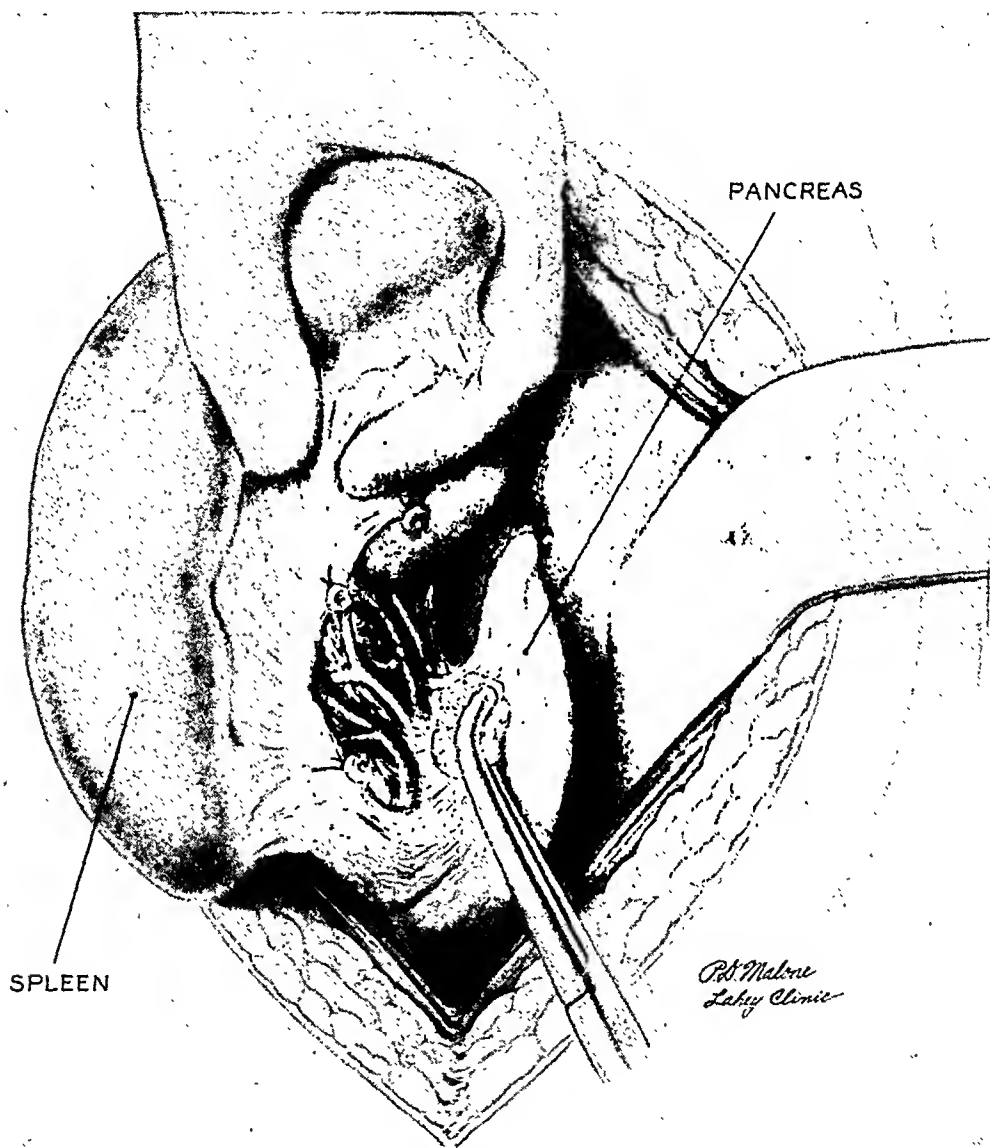


FIG. 3.—This is the standard method for accomplishing splenectomy rapidly by means of which the spleen is bluntly freed from its peritoneal attachments, turned forward into the wound, the tail of the pancreas wiped off and its pedicle controlled by clamps, mass ligature or individual ligature.

With the spleen out, it is not difficult to visualize the kidney region and determine whether or not there has been coincident injury to the renal vessels or to the kidney itself.

There is still another group of cases in which in recent years we have

employed splenectomy. This group includes the cases in which splenectomy, together with omentumectomy, is included in the operation of total gastrectomy in order to make the anastomosis of the jejunum to the esophagus easier, but primarily to increase the radicalness of total gastrectomy when done for early or extensive gastric malignant disease. We have employed splenectomy in about half of the 100 cases of this type in which we have done total gastrectomy.

It will be recalled that in most of the patients for whom total gastrectomy is employed, that is, those with lymphoma of the stomach, those with leiomyosarcomas involving most of the stomach, or those with carcinoma of the stomach of the linitis plastica type infiltrating usually a good part of the walls of the stomach, the malignancy as a rule involves all of the greater curvature and frequently runs upward to the entrance of the esophagus into the stomach. It is obvious that if the spleen be left behind and separated from the stomach by the ligation of the vasa brevia, there will be a section of omentum left behind attached to the spleen, there will be a severing of the blood supply along the upper part of the greater curvature of the stomach quite close to the gastric malignancy, and that by the removal of the spleen and not part but all of the omentum, a much more radical and extensive removal of the malignancy with a wider area about it can be accomplished. For this reason we believe that splenectomy, since it is apparently harmless from our experience with this good sized series of cases in which it has been added to total gastrectomy, is a very desirable procedure to employ in this condition.

There will be other conditions, such as transthoracic resection of the lower esophagus and cardia, also certain patients with diaphragmatic hernia in whom the spleen has migrated into the intrapleural hernia sac, and certain cases of diaphragmatic hernia, repaired from below, in which the removal of the spleen will make the exposure of the diaphragm and suture of the hernia in it much easier. There will even be cases of high ulcers of the lesser curvature in which, by removal of the spleen, a section of stomach can be so rotated downward that the high lesser curvature ulcers close to the esophagus can be removed and an adequate amount of stomach made available by this exposure and rotation to make it possible to do a partial gastrectomy rather than a total gastrectomy. In addition to this, there will be a few diverticula of the stomach high on the greater curvature in which removal of the spleen will make exposure and management of these lesions easier.

#### GROUP II

It is not as easy to discuss those indications for splenectomy which are related to what has been called the effects of hypersplenism upon the bone marrow and the peripheral blood cells, since hypersplenism may be either primary and of unknown etiology, as in idiopathic thrombocytopenia, idiopathic neutropenia or hemolytic anemia, or secondary as the result of in-

vasion of the spleen by tumor, inflammation or even associated with the splenomegalies of congestive splenomegaly. Those states are in addition much more complex as to the indications for splenectomy since many of the blood states which are caused by hyperspleens can and sometimes are brought about by toxic substances, certain drugs and some metabolic disturbances.

There is an important relationship existing between the spleen and the reticulo-endothelial system on the one hand and the bone marrow on the other. The spleen normally inhibits the bone marrow so as to exert a controlling influence on the output of blood cells produced by it. Under certain circumstances, this delicate balance is disturbed and the spleen may over-

TABLE I—*Indications for Splenectomy*

*Group I.*

1. Rupture of the spleen
2. Wandering spleen
3. Primary splenic tumors
4. To aid in exposure and radicalness in operations in left upper quadrant

*Group II.*

1. Congenital hemolytic anemia
2. Acquired hemolytic anemia  
(selected cases)
3. Idiopathic thrombocytopenic purpura
4. Idiopathic neutropenia
5. Primary splenic panhematocytopenia
6. Secondary splenic panhematocytopenia  
(selected cases)

*Group III.*

1. Congestive splenomegaly (selected cases)
2. Splenomegaly of unknown origin  
(selected cases)

inhibit the various cell-forming functions of the bone marrow or it may destroy cells more rapidly than it normally should. In some cases there is a combination of these two factors at play. These mechanisms are the basis for the indications for splenectomy in certain hematologic abnormalities.

It can no longer be said that there are only two clear-cut medical indications for splenectomy, namely congenital hemolytic anemia and idiopathic thrombocytopenic purpura. We must now add further medical indications: selected cases of acquired hemolytic anemia, idiopathic neutropenia, primary splenic panhematocytopenia, selected cases of secondary splenic panhematocytopenia, selected cases of congestive splenomegaly, and selected cases of splenomegaly of unknown origin (Table I).

*Congenital Hemolytic Anemia.* The hereditary abnormality in this disease leads to a change in many of the adult red blood cells by which they are

small in diameter but thicker than normal. These spherocytes are removed by the reticulo-endothelial system, of which the spleen is an important part, and their destruction leads to evidence of increased hemolysis with an increased output of urobilinogen in the urine and feces and hyperbilirubinemia. The anemia resulting from the destruction of red blood cells stimulates the bone marrow, which becomes overactive, the hyperplasticity being normoblastic in type. The reticulocytes in the peripheral blood are increased.

Splenectomy stops the greater part of this blood destruction, although it does not change the abnormality leading to the spherocytosis. If care is taken to remove accessory spleens, it is rare to have any return of anemia or jaundice. It is in this condition that splenectomy is most uniformly followed by good hematologic results.

We have had 20 such cases in the period from 1934 to 1947. There were no operative deaths. Three accessory spleens were found and removed in this series. Pigment gallstones were present in 25 per cent of the cases. Splenectomy resulted in complete cure of the anemia in 90 per cent of the cases and marked improvement in the other 10 per cent.

*Acquired Hemolytic Anemia.* This condition may be acute or chronic and may be secondary to a large number of diseases. The most important of these are: chemical toxins such as benzol, some parasitic diseases as malaria, certain bacterial infections, some cases of malignancy as leukemia, and idiopathic types in which abnormal agglutinins and hemolysins may be found. It is often impossible to predict whether splenectomy will be of any value in these cases. In general, it should not be done in malignancy, infections or parasitic disease. Rarely, a severe hemolytic anemia in a very chronic lymphatic leukemia might be benefited by splenectomy. Acute hemolytic anemia of the acquired type often responds favorably to splenectomy but does not always do so. The chronic hemolytic anemias demand detailed individual study and in selected cases removal of the spleen may prove beneficial. Results are uncertain, although occasionally spectacular. It should generally be considered the procedure of last resort in these conditions.

We have operated on six such patients (1934-1947), with no operative deaths but with excellent results in only one.

*Idiopathic Thrombocytopenic Purpura.* This hemorrhagic disease of unknown origin must be carefully distinguished from thrombocytopenic purpura of known cause. All drug contacts must be scrutinized and allergic phenomena considered. It is essential to study the bone marrow where the megakaryocytes in the idiopathic type will be plentiful and will show little platelet formation at their periphery. Bone marrow study will also rule out infiltrating disease, such as leukemia, which may cause thrombocytopenia by replacement. If the eosinophils are markedly increased, allergic types of thrombocytopenia must be suspected. If these precautions are strictly observed and the studies indicate a truly "idiopathic" type, results of splenec-



tomy will be good. However, under the best of circumstances relapses will occur, sometimes many years after operation.

The response to splenectomy is usually immediate but cases have been observed in which it was delayed and slow, although eventually adequate. The increased capillary fragility, prolonged bleeding time and low platelet count rapidly become normal and the purpura disappears. About 75 per cent of patients who undergo splenectomy for this condition remain permanently cured. In acute fulminating cases, splenectomy must be done as an emergency in order to avoid hemorrhage into vital organs. The discovery and removal of accessory spleens are of particular importance in this condition because if thrombocytopenic purpura should recur at a later date, the uncertainty of finding splenic tissue at operation makes any surgical procedure so dangerous as to be prohibitive. We have had 17 cases of this type with no operative mortality. Recurrences have taken place in three cases (17.6 per cent) and in two cases the response of the platelets was slow but eventually good. The other patients all responded rapidly and apparently permanently.

In patients with hemolytic anemia or with idiopathic thrombocytopenic purpura, once splenectomy has been settled upon it should be carried out without undue delay to avoid the occurrence of a critical state which can arise during the delay interval.

*Idiopathic Neutropenia.* In certain cases when the balance between bone marrow and spleen is upset and the normal inhibitory effect of the spleen is enhanced, the granulocytes alone may be affected, leading to a neutropenia. As in the other hematologic conditions already discussed, careful study of these cases is essential to rule out other known causes of neutropenia, such as drug and other chemical contacts, aleukemic leukemia, lymphoblastoma, and various infections. Again, the bone marrow picture will help to rule out these secondary causes of neutropenia and in the idiopathic type will be normal or will show a hyperplasia of the granulocytic cells with little change in the other elements.

It has only been in recent years that this disease has been established as a definite entity and now takes its place as another form of hypersplenism. The response to splenectomy is immediate and although enough time has not elapsed fully to evaluate this procedure, results appear to be long lasting.

*Primary Splenic Panhematocytopenia.* This form of hypersplenism involves all of the main cellular elements of the bone marrow and results in neutropenia, anemia and thrombocytopenia. The etiology of this syndrome is not known. Both congenital and acquired types have been described. Bone marrow studies in either type demonstrate hyperplasia involving the red cells, granulocytic and megakaryocytic elements. When the enlarged spleen is removed, there is a rapid return to normal hematologic values in the peripheral blood. Some cases are acute and require emergency splenectomy, while others are chronic and gradually become severe enough to require re-

peated transfusions to sustain life. Splenectomy is indicated in all cases of this syndrome when care has been taken to exclude known causes for pan-hematocytopenia.

*Secondary Splenic Panhematocytopenia.* A decrease in neutrophils, platelets and red blood cells in the peripheral blood may be secondary to a number of disease processes. In some way, as yet not understood, a spleen that is involved in almost any disease and becomes enlarged, particularly if the disease be of any lasting nature, may become hyperactive and exert an abnormal inhibiting effect on the cells of the bone marrow with or without an added increase in the destructive processes carried on by the spleen. For instance, Hodgkin's disease may be first discovered in this form when the spleen alone is involved and when the blood picture is only indirectly caused by the underlying disease coming as it does from a diseased spleen. Other forms of lymphoblastoma, chronic malaria, rheumatoid arthritis, congestive splenomegaly, sarcoidosis, tuberculosis, Gaucher's disease, and certain drug sensitivities, as in some cases of benzol poisoning, are all examples of the etiologic factors that may cause this syndrome.

Selected patients in this group respond well to splenectomy, the selection depending on the type of primary condition underlying the process, the severity of the hematologic abnormality, and the probable duration of life in the primary disease. Patients suffering from Hodgkin's disease with secondary hypersplenism of this panhematocytopenic type may rarely have no other manifestations of the disease for long periods of time and under such circumstances splenectomy is justified. This type of problem taxes the physician's judgment severely and it is sometimes impossible to judge whether the duration of life after splenectomy will be long enough to justify the procedure.

We have had seven cases of splenic panhematocytopenia. There has been no operative mortality in this group. The hematologic results have been excellent in four, good in one and fair in two.

### GROUP III

Under the third group comes congestive splenomegaly and the splenomegalies of unknown origin.

*Congestive Splenomegaly.* This condition arises whenever there is a partial or a total obstruction in the splenic vein or any portion of the portal system at or above the level of the splenic vein. Such obstruction results in hypertension within the portal system behind the obstruction and to an engorged collateral circulation that often menaces life by severe hemorrhage into the stomach or esophagus. The most common site of portal obstruction is within the liver itself and is the result of cirrhosis. Other less common etiologic factors in this syndrome are congenital abnormalities of the portal system, rare cases of *Schistosomiasis mansoni* and thrombosis of the splenic vein. When portal cirrhosis is the primary factor, hepatic failure or hemorrhage from varices may be the terminal event.

In addition to the danger of hemorrhage from varices, the enlarged spleen often eventually leads to panhematocytopenia with its bad effect on the general well being of the patient. Banti originally implied that a splenic hormone was to blame for the liver cirrhosis in these cases and this theory has never been completely disproved. Careful evaluation of the patient with this syndrome is essential and a decision for or against splenectomy is often difficult to make. In general, it should be said that any patient with congestive splenomegaly should have the enlarged spleen removed if he is able to stand the operative procedure. By this means, from 25 to 40 per cent of the blood entering the portal circuit can be removed and the hypersplenic effects of the enlarged spleen abolished. Unfortunately, we often see these patients only after they are far advanced in their disease, and they are often desperate risks. Only after extensive study of the liver function, prolonged medical preparation, and careful weighing of the pros and cons in the individual case can a decision be reached. If we are to help more of these patients, it is necessary that we see them before the late phases of the disease when liver function has been so badly damaged, varices so widely established and secondary hematologic changes so far advanced.

Splenectomy should be performed as soon as the diagnosis has been established and the condition of the patient permits. We have had 25 cases of congestive splenomegaly in this series (1934 to 1947); there have been two operative deaths, a mortality of 8 per cent. These represent the only operative deaths in the entire series. Postoperative complications are frequent and vary from many types of infection to liver failure.

Of the 14 patients who had gastro-intestinal bleeding preoperatively, 12 could be followed postoperatively and three of these had recurrent hemorrhage, one eight months after operation, one three and one quarter years after operation and one three and three quarter years after operation. The course of the remaining nine patients was followed from three months to seven years with an average follow-up of 26 months, and they had no postoperative bleeding. Hematologically, the results have been uniformly good with return to normal blood values.

*Splenomegaly of Unknown Origin.* Routine careful physical examination will uncover a considerable number of cases of unexplained splenomegaly in the course of any physician's practice. These cases tax his diagnostic acumen and a number will remain unexplained after exhaustive study is completed. If, after six months' observation, the spleen enlarges or remains unchanged and the cause is still unknown, it should be removed. In the temperate zones many cases of early congestive splenomegaly will be discovered in this way, and when removed at this stage will greatly delay or entirely prevent the development of varices. Some examples of malignant tumors primary in the spleen will be found and occasionally removed before spread to other parts of the body has taken place. Removal and study of these spleens undiagnosed before operation will do much to increase our

knowledge of this organ, its pathology and its pathologic physiology. It is understood, however, and this point cannot be overemphasized, that splenectomy must never be performed until all studies have been exhausted in attempting to make a diagnosis and above all, a sincere effort made by a competent observer to rule out definite contraindications to splenectomy.

#### CONTRAINDICATIONS

It is essential that the spleen not be removed in cases of agnogenic myeloid metaplasia because in this condition much of the bone marrow function of forming blood cells has been transferred from the bone marrow to the spleen and removal of this organ may be rapidly fatal. Competent hematologic study and bone marrow observation will quickly establish this diagnosis and any thought of splenectomy must be dismissed. With rare exceptions, splenectomy in cases of leukemia and lymphoblastoma with splenomegaly should be avoided. The exceptions include rare panhematocytopenias or hemolytic anemias of severe degree caused by hypersplenism in some of these cases. They also include cases in which the disease may still be limited to the spleen but such cases are very rare indeed. The spleen should not be removed in polycythemia vera although rarely a case is seen in which the influence of the enlarged spleen is such as to inhibit the output of a normal number of cellular elements. It is most unusual to find splenomegalies in infections in which splenectomy is justified, although rarely the hypersplenic effect is such as to demand careful consideration of this procedure. In general, patients with paroxysmal nocturnal hemoglobinuria do poorly after splenectomy and patients with Mediterranean and sickle cell anemias are also not helped by the procedure.

The technical complications of splenectomy in patients with congestive splenomegaly in which marked perisplenitis exists are of such seriousness and the benefits so problematical as to contraindicate its employment when this state is found.

#### COMPLICATIONS

The complications of splenectomy are hemorrhage, thrombosis and infection. Hemorrhage may arise from the surgical bed if a vessel comes loose or it may arise from a general oozing secondary to severe liver damage and a resulting hypoprothrombinemia. This complication sometimes follows splenectomy for congestive splenomegaly associated with severe liver damage and is of bad prognostic significance. Thrombosis occurs more readily after splenectomy than after other surgical procedures because of the rapid and excessive rise in platelets that occurs immediately following operation. Careful observation of the platelet count and the institution of anticoagulant therapy in certain cases will reduce this complication to a minimum. Infection of various types may follow splenectomy particularly in cases of congestive splenomegaly associated with severe liver damage, and in these cases modern potent antibiotics should be used

prophylactically. Liver failure may follow and attempts should be made to anticipate this with present day methods.

Table II demonstrates the frequency of complications in congestive splenomegaly as compared to other reasons for splenectomy. Table III shows the type of complications encountered in our series.

#### TECHNICAL CONSIDERATIONS

Many methods of doing splenectomy have been developed and published but in general the approach to splenectomy divides itself again into three

TABLE II—*Frequency of Complications of Splenectomy*  
(1934-1947)

Congenital hemolytic anemia (20 cases).....	1
Idiopathic thrombocytopenic purpura (17 cases).....	3
Acquired hemolytic anemia (6 cases).....	2
Congestive splenomegaly (25 cases).....	19
Cysts (4 cases).....	0
Miscellaneous (4 cases) .....	0
	<hr/>
Total .....	25

TABLE III—*Type of Complications of Splenectomy*  
(1934-1947)

Atelectasis .....	4
Subdiaphragmatic abscess .....	3
Thrombophlebitis .....	4
Ascites .....	2
Hemorrhage from liver failure .....	3
Miscellaneous infections .....	7
Hemolytic crisis.....	1
Diarrhea (question of etiology) .....	1
	<hr/>
Total .....	25

distinct plans: (1) preliminary ligation of the splenic artery close to its origin; (2) the deliberate exposure of the splenic vessels along the upper edge of the pancreas and as they enter the hilum of the spleen by careful and accurate exposure, as shown in Figure 2, through the gastrocolic omentum and (3) the rapid method of freeing the spleen from its attachments to the lateral and posterior abdominal wall by blunt separation of the spleen from these peritoneal attachments with the fingers. Each of these technical approaches to splenectomy has advantages under different circumstances.

In the spleen of enormous size and in those with any degree of perisplenitis, the method shown in Figure 1 in which the splenic artery is ligated close to its source of origin has great advantages controlling, as it does,

the main arterial supply to the spleen. In those patients with blood changes not in acutely critical states in whom careful and deliberate anatomical exposure can be obtained and in whom, because of their general condition, the matter of time is not important, the method shown in Figure 2 is most applicable. By this plan of visualization, the vascular structures entering the hilum of the spleen can be clearly visualized and individually and accurately ligated. All operations with this exposure can be done neatly in a dry field, and with this exposure, careful search, as is so often necessary, can be made for accessory spleens.

TABLE IV—*Results of Splenectomy*

Disease	No. of Cases	Good	Fair	Poor	No follow- up avail-	
					Deaths	able
Congenital hemolytic anemia . . . . .	20	18	..	..	0	2
Idiopathic thrombocytopenic purpura	17	13	..	3	0	1
Acquired hemolytic anemia . . . . .	6	1	..	5*	0	..
Panhematocytopenia . . . . .	7	5	2	..	0	..
Congestive splenomegaly . . . . .	25	17	3	2	2	1
Cysts . . . . .	4	4	..	..	0	..
Miscellaneous . . . . .	4	2	..	..	0	2
Total . . . . .	83	60	5	10	2	6

\* This group can be improved in the light of our present knowledge and by being more critical in the selection of cases.

In those patients in a more urgent state, such as patients in whom rupture of the spleen has occurred, patients in whom splenectomy must be done for serious blood changes and who are in critical states, the method shown in Figure 3, by which the spleen can be rapidly delivered, the tail of the pancreas separated and the pedicle clamped or ligated, can very materially save both time and blood. This type of splenectomy, however, does not lend itself as well to careful search for accessory spleens as does that shown in Figure 2.

*Splenectomy.* The operation of splenectomy has now been performed for so many years, so many men have done it and it has been so well standardized that, other than to illustrate these three methods of approach, we do not believe further discussion of the technical considerations of splenectomy are necessary.

We have employed a good sized left rectus, longitudinal, transrectus incision in all of these cases, but realize that tastes in incisions vary and that there is but one point involved in any discussion of them, namely, that they should be of sufficient length to make it possible to visualize the anatomy and to do surgically anatomic procedures.

## COMMENT

The decision for splenectomy in any given case is not to be entertained lightly. The operation may be technically extremely difficult and the post-operative path strewn with obstacles. The careful selection of cases is essential. Complete medical and hematologic study will help in this selection. A mistaken diagnosis may put the patient through a serious operation without benefit or an error in judgment cost him his life. Only by the closest cooperation of the surgeon and the internist can the greatest benefit be derived or a catastrophe averted.

With the spreading knowledge of the increased number of indications for splenectomy, the dangers of this procedure may be overlooked and the contraindications misunderstood. This could result in placing a valuable procedure in disrepute.

If our knowledge of splenectomy, its indications and contraindications is to advance, it is essential that the interest of physicians and surgeons be aroused in recognizing splenomegaly in its early stages at a time when the greatest good is to be derived from its removal (Table IV).

## SUMMARY

1. We have discussed the three groups of conditions in which splenectomy is indicated.

2. The removal of the spleen to facilitate the ease of total gastrectomy and to increase the radicalness of this procedure is recommended.

3. The hematologic indications and contraindications for splenectomy are discussed.

4. Congestive spleens, when the patient's condition will permit it, should be removed to prevent future complications or to improve such complications if they already exist.

5. Enlarged spleens of unknown etiology after adequate and prolonged study should be removed.

6. The contraindications are specific and must be observed.

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DISCUSSION.—DR. GEORGE M. CURTIS, Columbus, Ohio: In a considerable series of splenectomies for congenital hemolytic icterus and for thrombocytopenic purpura we have had eight recurrences; three in congenital hemolytic icterus and five in thrombocytopenic purpura. The first two have been reported in the Annals (Vol. 123, p. 276, Feb. 1946). In the third patient, with thrombocytopenic purpura, there was a definite recurrence after two years. An exploratory operation was done and no accessory spleen was found in the ordinary or even in the unusual places. As a consequence we recalled the embryology of the spleen, which develops from the left half of the dorsomesogastrium, and that sometimes this touches the genital ridge attached to the adjacent Wolffian body, just to the left. When the Wolffian body descends, and particularly when the gonad descends, it may thus carry down with it a bit of spleen. That is the reason why the spleen is sometimes found within the

tunica vaginalis or attached to the ovary. In fact, there are reports which show a strand of splenic tissue extending from the major spleen down along the left posterior gutter.

Because of these facts we opened the posterior gutter in this third patient and found a 2 cm. accessory spleen retroperitoneally, behind the lower pole of the left kidney. The fourth patient, a girl with recurrence of thrombocytopenic purpura, was explored and no accessory spleen was found. However, we found a remarkable enlargement of the mesenteric lymph nodes, together with enlargement of the retroperitoneal and celiac nodes.

In the fifth case we had a similar experience. In the sixth, a patient with congenital hemolytic icterus, we were also unable to find an accessory spleen. However, the liver presented the color usually characteristic of the spleen. Biopsy of the left lobe of the liver revealed a remarkable reticuloendotheliosis involving particularly the von Kupffer cells, some of which could be shown to be phagocytic. There was also in this patient a moderate lymphadenosis.

In the seventh patient, operated upon by one of my associates, there was recurrence of thrombocytopenic purpura and a small accessory spleen was found along the greater curvature of the stomach. In the eighth and last, recurrence of congenital hemolytic icterus, it was possible for my colleague, Dean Charles A. Doan, to demonstrate radiographically the accessory spleen by the use of thorium. This was found just above the upper pole of the left kidney. It was removed recently and we are not yet certain of the end result.

Thus in eight patients with recurrence we have found in five instances an accessory spleen, in three a lymphadenosis with reticuloendotheliosis and in one an associated hyperplasia of the von Kupffer cells of the liver.

Dr. Lahey remarked about the end results of splenectomy for idiopathic neutropenia. I removed the spleen in the first case recorded in October, 1939 (*Ann. Int. Med.*, Vol. 16, p. 1097, June, 1942). This patient was hospitalized last summer for removal of a pilonidal cyst, and careful studies were made. So far as we could determine there was no residual hematologic disturbance. Her neutrophils had remained normal since the splenectomy.

Dr. OWEN H. WANGENSTEEN, Minneapolis: I wish to speak on a technical point. Dr. Lahey has been an exponent of removal of the spleen in total gastrectomy. Over a period of several years, I have been aware of the circumstance that a dry wound does not regularly accompany total gastrectomy. The reason for fluid collections in the vicinity of the esophagojejunal anastomosis was not apparent; but because of this occurrence over a period of approximately two years, I have been putting in an air-vent suction of the sump or Chaffin variety down to the splenic bed after excision of the spleen and establishment of the esophagojejunal anastomosis. In a number of instances, considerable fluid has drained away—as much as 200 to 500 cc. per day, and occasionally even more; as much as 800 cc. drainage of fluid through such an air vent suction drain has been recorded in a single day. Drainage of this amount of fluid is not observed ordinarily until several days (5 to 8) have elapsed since the total gastrectomy and splenectomy were done.

A year ago, one of my associates, Dr. Ivan Baronofsky, made an unusual and startling observation concerning the nature of such fluid drainage following such operative procedure. It occurred to him that this fluid might be pancreatic juice—and such it proved to be; in any case the fluid contained as much amylase as pure pancreatic juice.

Large mortalities have been recorded attending the operation of total gastrectomy. The maintenance of a dry wound is an important item in the healing of any wound. And as surgeons are aware, the accumulation of fluid about a gastro-intestinal anastomosis does invite a subphrenic abscess; moreover, a subphrenic abscess is a more



serious situation in the presence of a gastro-intestinal suture line, in that the abscess may erode the suture line and invite fistula. Routine placement of an air vent suction drain down to the plenic bed behind the esophagojejunal anastomosis, together with employment of the jejunal wall as a posterior buttress for the posterior wall of the esophagus — these two measures have made it possible in our clinic to perform total gastrectomy with a risk which is not far out of line with that of partial gastric resection for cancer.

Such drainage of pancreatic fluid has been observed following excision of large spleens without other coincidental operative procedures. In other words, splenectomy may be accompanied by a temporary pancreatic fistula. Moreover, the febrile episodes observed occasionally after splenectomy may have their origin in such an explanation.

There are two possibilities to account for their occurrence: (1) Injury to the blood supply of the tail of the pancreas in the ligature of the splenic vessels; (2) Pancreatic ducts may actually terminate occasionally in the hilum of the spleen. Dr. Baronofsky is studying the problem at the present time. In any case, external drainage of pancreatic fluid attending splenectomy alone or splenectomy and total gastrectomy, has been observed several times in this clinic—an occurrence which suggests that an air vent suction drain probably should be employed regularly in splenectomy.

DR. JOHN W. NORCROSS, Boston (closing): I should like to emphasize what Dr. Lahey has already said concerning the excellent opportunity for co-operation between surgeon and physician in the handling of patients with splenomegaly. After careful medical study, the internist can usually establish the hematologic diagnosis.

Operative risk is often difficult to evaluate, particularly in cases of congestive splenomegaly. In this important group, if the patient can be successfully carried through the procedure and the immediate postoperative stage, he will usually derive definite benefit from the operation. In this condition, removal of the spleen will decrease the volume of blood entering the portal circuit by from 25 to 40 per cent and, accordingly, will decrease the danger of hemorrhage from engorged varices. Splenectomy will also abolish the hypersplenic effect on the bone marrow in these cases when it is present.

Careful management of the postoperative course is particularly important in this group of patients with congestive splenomegaly. The danger of infection is great, but with our present antibiotics we are in much better position than formerly to control this danger effectively. Hemorrhage of the type that comes from severe damage to liver function and which is related to the inability of the failing liver to manufacture prothrombin, can be controlled only by multiple fresh blood transfusions. The careful use of modern anticoagulants, heparin and dicoumarol, makes it possible to control impending thrombosis in the portal system in cases in which the platelet count rises to extremely high figures after splenectomy.

If we are to treat patients with splenomegaly most effectively, it is essential that such cases be recognized early, and careful palpation for an enlarged spleen should be a part of every physical examination. When patients with splenomegaly of undetermined etiology have been studied carefully over a period of several months, and if the contraindications can be ruled out definitely, splenectomy is justified.

I should like to stress the contraindications to splenectomy. First and foremost of these is the splenomegaly of agnogenic myeloid metaplasia. In this condition the spleen has taken up the function of forming the elements of the peripheral blood which are normally made in the bone marrow. Under such circumstances it is dangerous and often fatal to remove the spleen because this organ is the main source of blood cell formation. In the splenomegaly of chronic infectious conditions, only on very rare occasions should splenectomy be carried out. In general, patients with malignant conditions involving the spleen should not be subjected to splenectomy. Enlarged spleens in cases of polycythemia should not be removed.

# THE TREATMENT OF RENAL INSUFFICIENCY IN THE SURGICAL PATIENT\*

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ANY PLAN OF THERAPY for the patient with acute renal insufficiency of the lower nephron type should be directed at maintaining survival of the patient until such a time that adequate recovery of renal function ensues. This time interval is undoubtedly related to the degree of renal tubular and interstitial pathology present subsequent to the initial injury. In the clinical experience of the authors, this interval has varied between seven and 14 days. It may be shorter or longer since it will be modified by other factors present. (Table I.)

Several methods of internal or external hemodialysis have been suggested as a substitute for renal function during the period of renal insufficiency. (Peritoneal lavage, artificial kidney, gastro-intestinal lavage.) The main objections to such methods usually revolve around: (1) the technical difficulties involved, (2) the complications produced, or, (3) the inability of any particular method adequately to substitute for renal function. The authors have had no experience with internal or external hemodialysis.

A simple conservative plan of management which has proven successful in the last several cases of acute renal insufficiency at the University Hospital is presented. It requires no particular technical equipment and entails only a minimum of laboratory aid. The plan of management is based entirely upon the time interval required for renal tubular healing to occur following injury, and upon the premise that the patient may be maintained in a satisfactory clinical condition during this period by very conservative measures.

It has been adequately demonstrated that serious degrees of renal failure may develop following transfusion reactions, shock or prolonged hypotension, burns, various types of injuries, and from numerous other causes. The subsequent morbidity and mortality in such patients have been high in spite of the use of various forms of therapy.

Malloy<sup>1</sup>, Lucké<sup>2</sup>, and others, on the basis of material obtained at autopsy from known cases of renal failure following injury, transfusion reaction, etc., have pointed out that the significant pathologic changes in the renal parenchyma, while not necessarily specific, are practically constant in location. These lesions are for the most part confined primarily to the distal tubular segments of the nephron units. They are often reversible in that healing of the areas

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\* Read before the American Surgical Association, Quebec City, Quebec, May 27, 1948.

of tubular damage may ensue with recovery of adequate renal function and survival of the patient.

Muirhead, et al<sup>3</sup>, have pointed out that the poor past record in the management of these cases may be attributed to one of two general causes: (1) the injury sustained by the patient is so great as to preclude the success of any type of management or, (2) the type of management in the past has not been conducive to the proper recovery of these cases. (The primary disease present in the patient, such as a far advanced carcinoma of the stomach with perforation, may preclude ultimate recovery from the primary disease, but does not necessarily prevent the recovery from renal failure which may have developed in such a patient). Cases 6 and 10 are examples of these situations.

TABLE I.—*Electrolyte Excretion Preceding and During the Phase of Diuresis.*

Patient	Day	Urine Volume cc.	—Urine*—		—Serum*—		Plasma Electrolyte Volume or 0.9% NaCl Equivalent**
			Na	Cl	Na	Cl	
Case 2	11-12-13	5325	90.8	78.0	120	87	49.8 Gm. NaCl — 5.53 liters of 0.9% NaCl in 9.4 liters urine. Equivalent to 6.8 liters E.C.F. on the basis of Cl, or 5.86 liters on the basis of Na.
	14	4100	89.7	73.0	...	...	
	9	240	...	42.3	139.7	98.5	0.097 liters — 0.4 Gm. NaCl.
Case 1	14	2000	...	46.0	133.7	93.3	0.876 liters — 5.38 Gm. NaCl.
	20	8075	...	73.2	135.4	98.2	34.6 Gm. NaCl — 3844 cc. 0.9% NaCl or 5.63 liters E.C.F. equivalent.
Case 4	15	3200	90.2	...	...	...	16.88 Gm. NaCl — 1875 cc. 0.9% NaCl or 1.99 liters E.C.F. on basis of Na.

\* M. Eq/L.

\*\* Estimated on the basis of Na — 145 M. eq./liter E.C.F. and Cl — 105 M. eq./L. E.C.F.

Renal tubular epithelium which has been the site of injury may heal within a relatively brief period of time. Evidences of such healing have been observed in autopsy material in our own series of cases as early as the 8th day. Clinically, recovery of the ability of the kidney to excrete urine has usually occurred in our own experience within seven to 14 days. It has been assumed that this onset of diuresis reflects progress in healing of the renal parenchymal lesion.

#### THE MANAGEMENT OF ACUTE RENAL INSUFFICIENCY\*

The plan of therapy falls into three phases, (1) the period of shock, hemolysis, injury, etc., (2) the period of renal insufficiency lasting one to 14 days, and (3) the period of recovery diuresis which ordinarily lasts five to seven days. The actual treatment varies considerably during these three phases. During the period of shock or hypotension, treatment consists of the measures usually employed, i.e. blood transfusions, oxygen, intravenous fluids,

\* Excluding internal or external hemodialysis. This three-phase plan is similar to that suggested by Muirhead.<sup>3</sup>

# RENAL INSUFFICIENCY

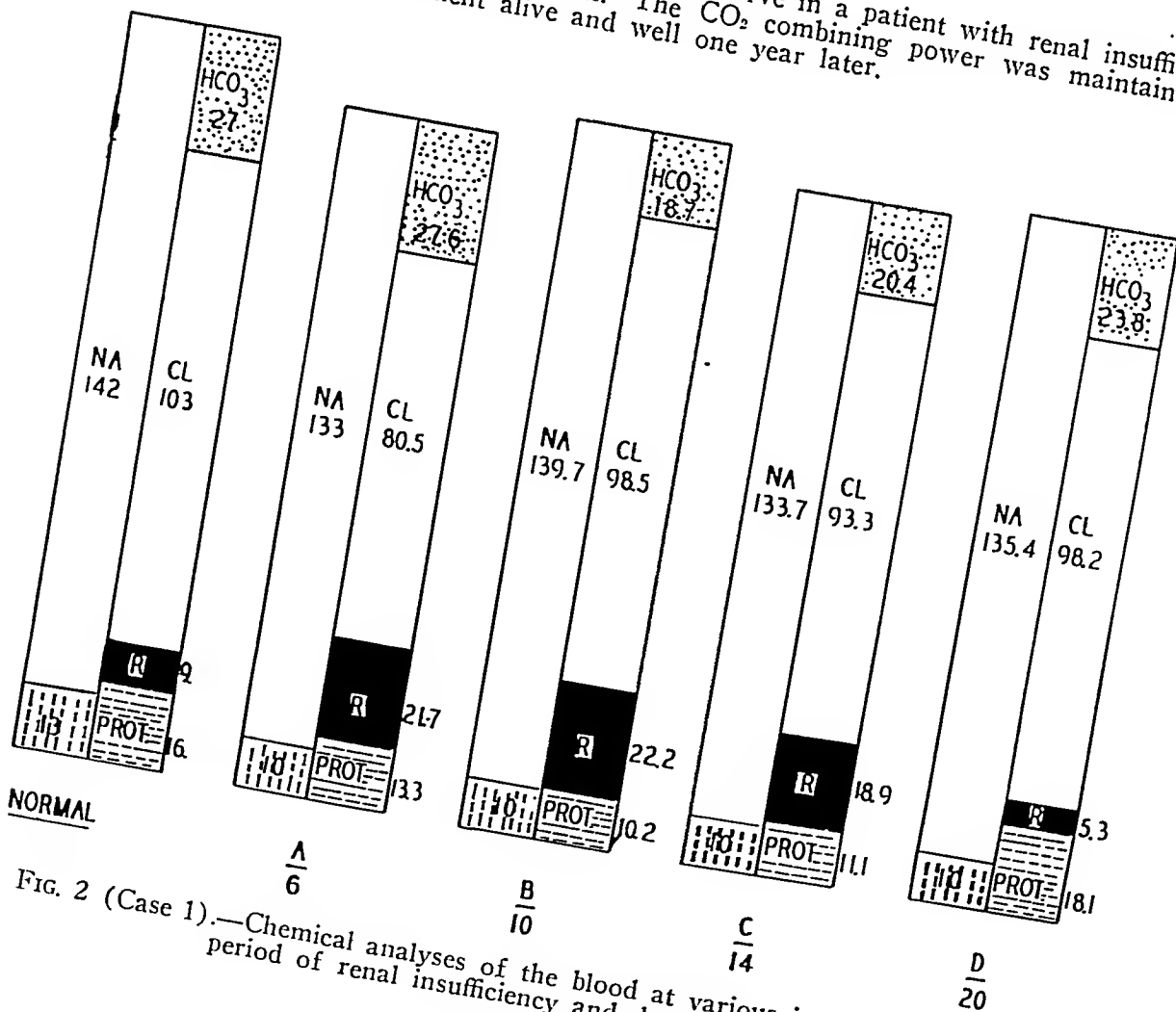
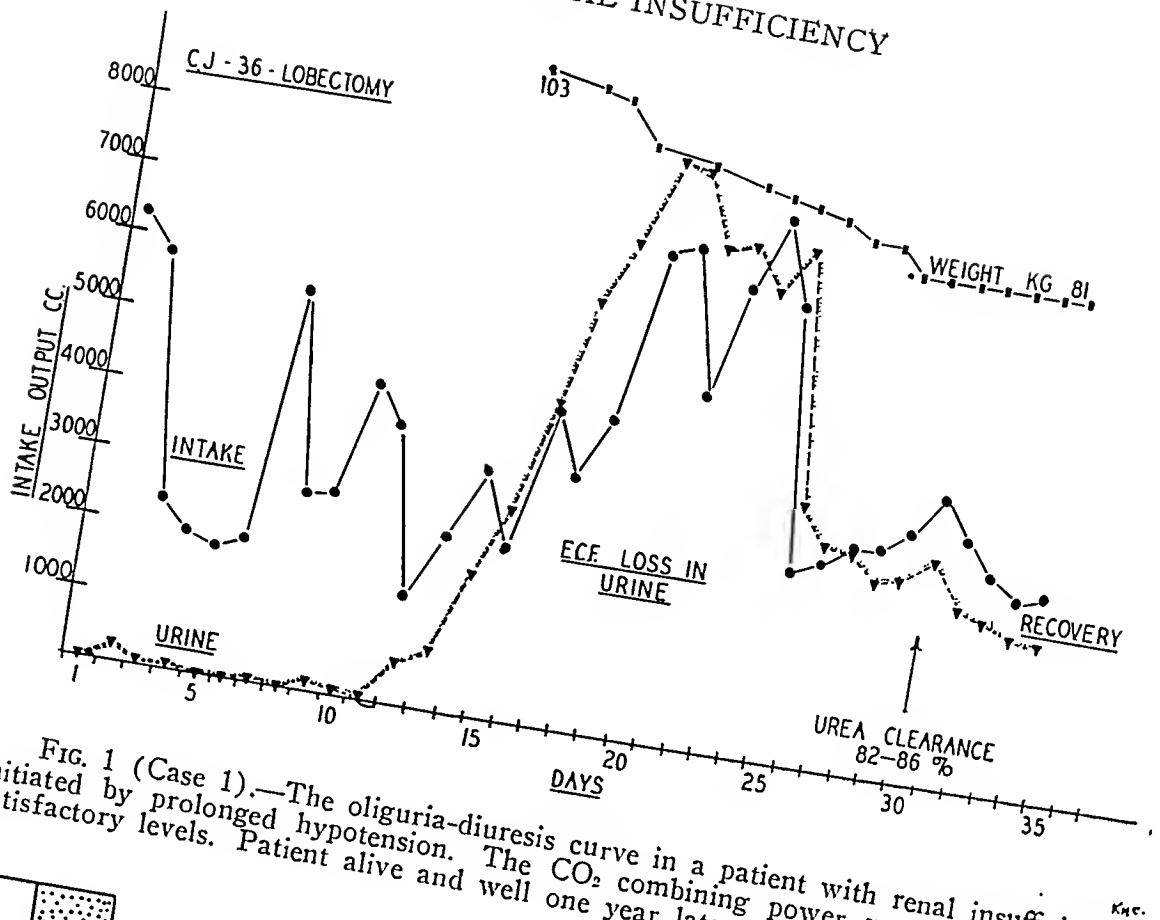


FIG. 2 (Case 1).—Chemical analyses of the blood at various intervals during the period of renal insufficiency and during recovery.

TABLE II.—Initiating and Perpetuating Factors in 10 Cases of Lower Nephron Nephrosis.

Case	Termination	Recovery Renal Function	Transfusion Reaction	Initiating Shock or Hypotension	Initiating and Perpetuating Factors Present	Previous Renal Damage	Sulfa Therapy
1	Recovery	+	?	Moderate	Injury or Operation	—	—
2	Recovery	+	+	Mild	Small Empyema	—	—
3	Recovery	+	+	Moderate	Wound	—	—
4	Fatal	—	?	Severe	Lobectomy	?	—
5	Recovery	+	+	Mild	Gastrectomy	Hydronephrosis II	—
6	Fatal	—	—	Mild	Cystectomy	Moderate Hydronephrosis	?
7	Fatal	—	—	Mild	rhage	—	—
8	Fatal	Partial	—	Severe	Splanchnicectomy	—	—
9	Fatal	—	—	Severe	Fracture	—	—
10	Fatal	+	+	Moderate	Choledocho-Duodenostomy	Arteriosclerosis	+
					Esophago-Gastrectomy	Aplastic Left Kidney	+
					Amputation	—	—
					Pyothorax	Arteriosclerosis	+
					Gas Gangrene Perforation	—	—
					Ca Stomach	—	—

Cases 1-5 and 10 were treated by the three-phase plan of management described in this article. Cases 6-9 were random selections of patients from the various surgical services prior to the introduction of this plan of therapy where autopsy material was available.

etc. As soon as renal insufficiency becomes manifest, a sample of blood from the patient is sent to the blood bank for re-checking of the original cross match, if this is thought to be the source of the difficulty, extra-renal parenchymal urinary tract obstruction is excluded to the satisfaction of the attending staff, and the total fluid intake of the patient is immediately limited to the daily calculated insensible loss, (perspiration and respiration). This will vary between 1000 and 1800 cc. in the afebrile patient and consists of water given orally or 5% glucose in distilled water intravenously. This restriction of total fluid intake is enforced until adequate urine output ensues.

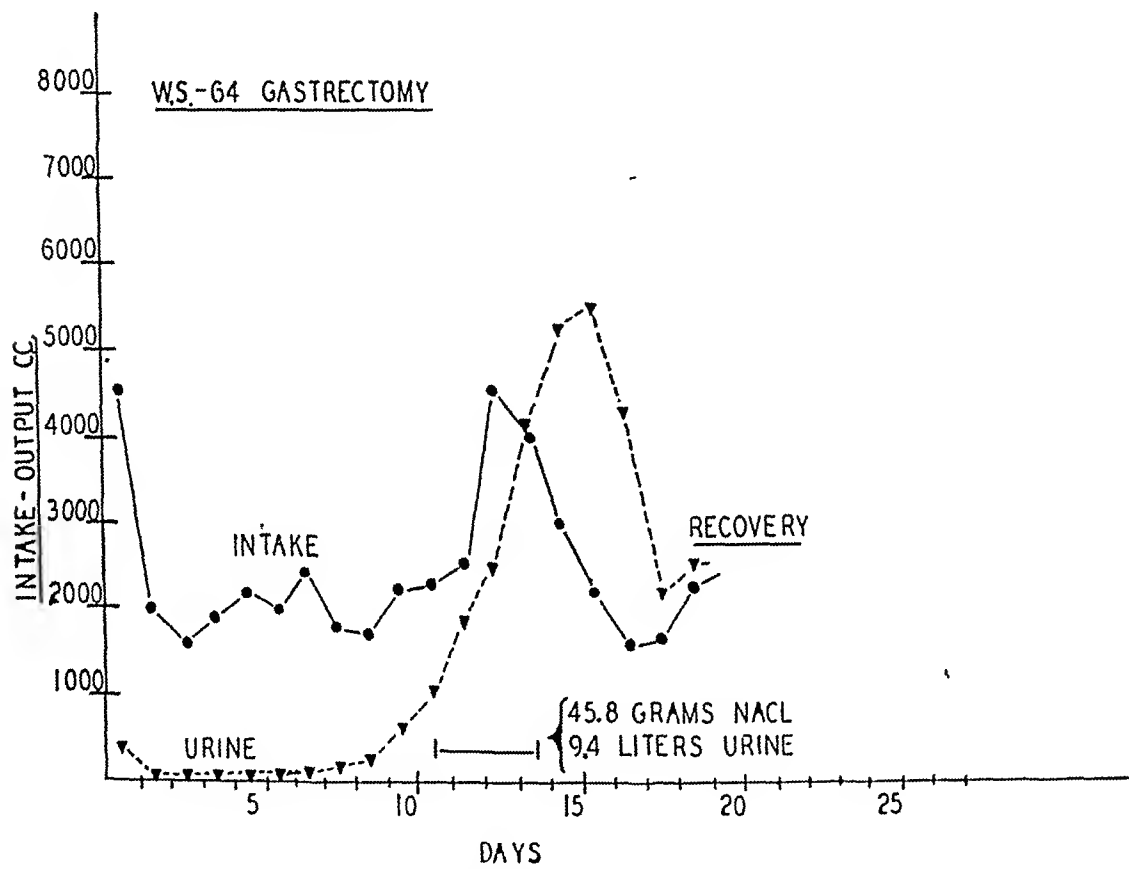


FIG. 3 (Case 2).—Characteristic oliguria-diuresis curve in a patient with anuria following a hemolytic transfusion reaction. Subtotal gastrectomy for carcinoma. Recovery. Note the declination of intake and the increment of urine output during the phase of recovery diuresis.

Periodic blood NPN and carbon-dioxide combining power determinations are made throughout the period of renal insufficiency. Such determinations are optional but at the same time desirable. Correction of the  $\text{CO}_2$  combining power is carried out only when levels of 40 volumes % or lower are reached. This is achieved by the use of sodium bicarbonate orally or sodium lactate (one-sixth molar) intravenously. Such measures modify the  $\text{CO}_2$  combining power without necessarily correcting the actual cause of the acidosis. It should be recognized that the use of these solutions leads to the introduction of sodium salts in the presence of renal insufficiency.

Calcium gluconate or levulinate intravenously in 10 cc. doses is employed daily throughout the period of renal insufficiency to allay the development of

the signs and symptoms of tetany. This measure is also optional. The diet given these patients has varied considerably and the authors have noted no untoward effects from either high protein intake or restriction. The salt content of the diet should be restricted to 200-800 mg/day until diuresis occurs. If a positive fluid load, i.e. endema, has occurred either during or prior to treatment, rigid restriction of salt and fluid intake is employed until the positive fluid load is corrected.

During the third phase of treatment (recovery diuresis) an interesting paradox may occur. Recovery of renal function is made apparent by the

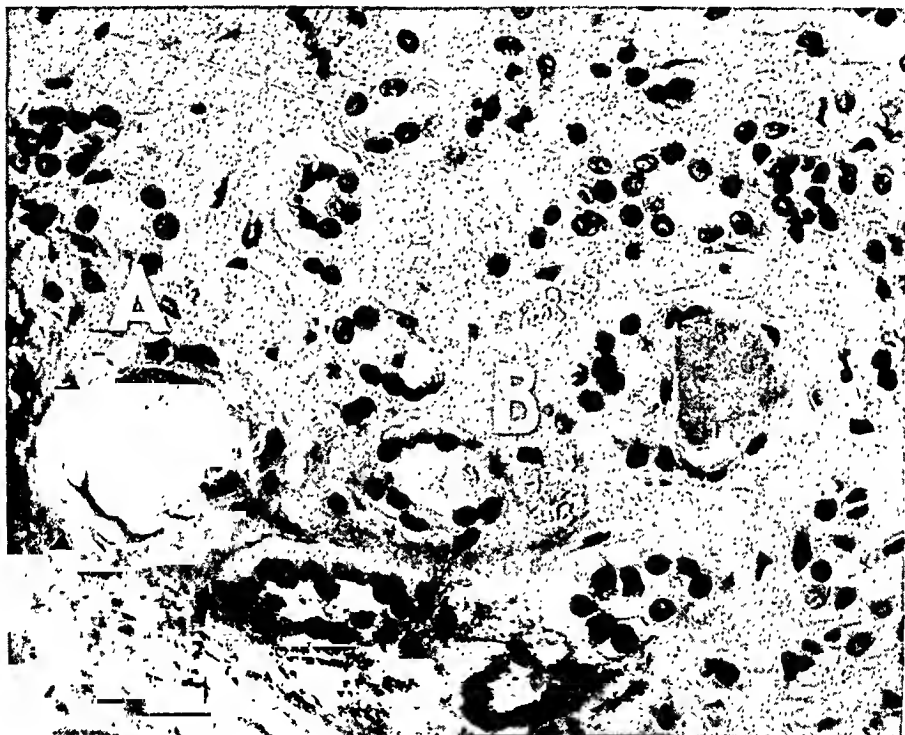


FIG. 4 (Case 10).—Hyaline casts in the tubules of the medulla. The pyknosis of the nuclei (A,B) are indicative of regeneration of epithelium in a patient with a perforated carcinoma of the stomach who died 14 days following a transfusion reaction. Recovery diuresis present at the time of death.

daily increase in urine output. (Figs. 1, 2, 3). At the same time, abnormal water and electrolyte losses in this urine may place the life of the patient in jeopardy from acute dehydration or hypopotassemia (Table II). Therapy at this time is therefore directed at accurate replacement of urinary losses of sodium, potassium<sup>3</sup>, and water. This is mandatory if acute dehydration is to be prevented. Urine analyses for sodium, potassium and chloride at this time are desirable. The method of replacement of salt and water losses during this period has been achieved through the use of Ringer's Solution intravenously and/or a 0.5% salt solution orally.\* Inasmuch as it is extremely difficult to

\* NaCl—4.0 Gm./liter plus NaHCO<sub>3</sub> 1.0 Gm./liter.

either anticipate or replace a urine output of eight or nine liters in 24 hours, careful attention is given to the daily increment in urine output once the phase of recovery diuresis has become manifest. When the urine output reaches a level of 5 liters or more daily, an equivalent amount of Ringer's solution intravenously is given. Any difference between output and intake is paralleled by an oral intake of salt solution equivalent to the amount of urine passed with each urination. Decreasing the fluid intake has not reduced the increment in urine output even when such a plan has been carried out over a four

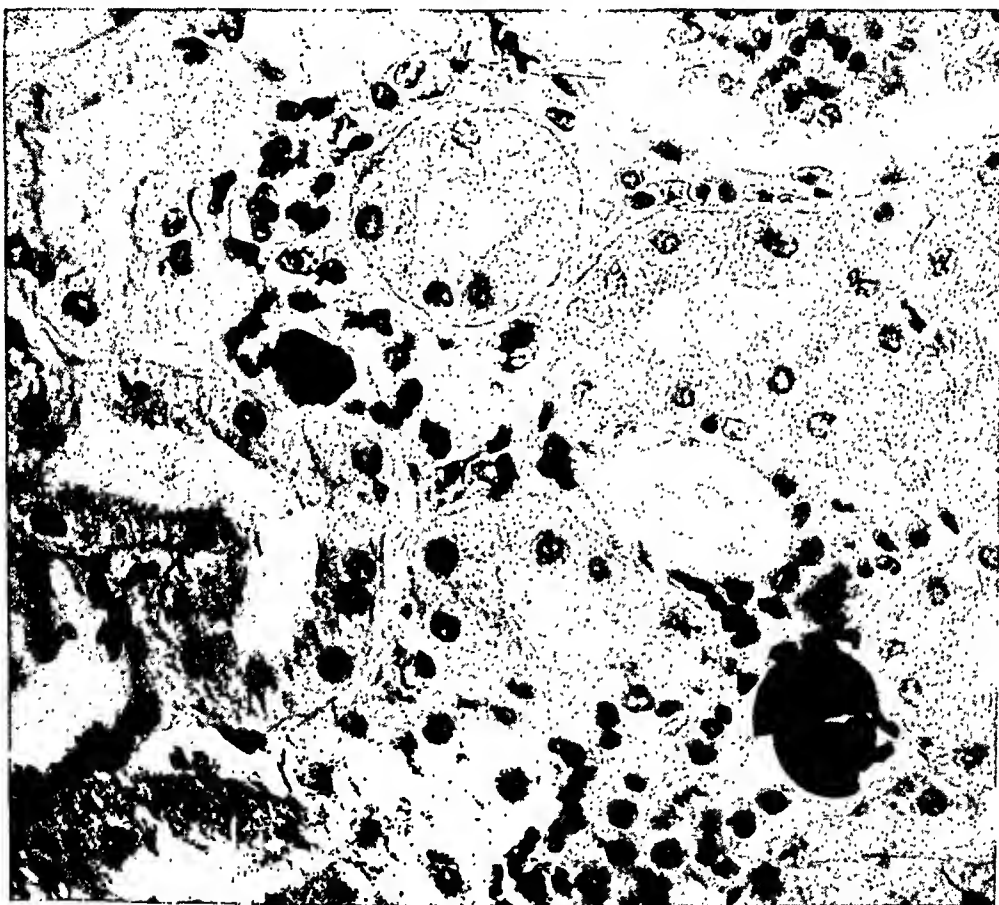


FIG. 5 (Case 10).—Crystals in the distal convoluted tubules. Cloudy swelling of epithelium in the proximal convoluted tubules with precipitated protein in the lumen.

day period. (Fig. 3). The degree of recovery diuresis will vary tremendously with different patients, in some instances being quite marked, in others, of little consequence.

Following restitution of the urine output to normal levels, renal function tests are carried out. These tests are optional, but do reflect the degree of recovery which has taken place. The blood NPN has not returned to normal levels, in the experience of the authors, for some 28-35 days after the initiation of renal insufficiency. Muirhead<sup>3</sup> has pointed out the inability of the kidneys under these circumstances adequately to excrete nitrogenous waste



materials despite a recovery diuresis. In cases 1, 2, 3, 4, the blood NPN reached a peak increment and then a descent to lower values between the 12th and 14th day in each case. Weight loss during the period of diuresis has been quite striking in two of the patients in the recovery group (Cases I, II).

#### CASE HISTORIES

Patients 1, 2, 3, 4, 5 and 10 were treated by the three phase plan of management. Patients 6, 7, 8, and 9 represented previous fatalities on the

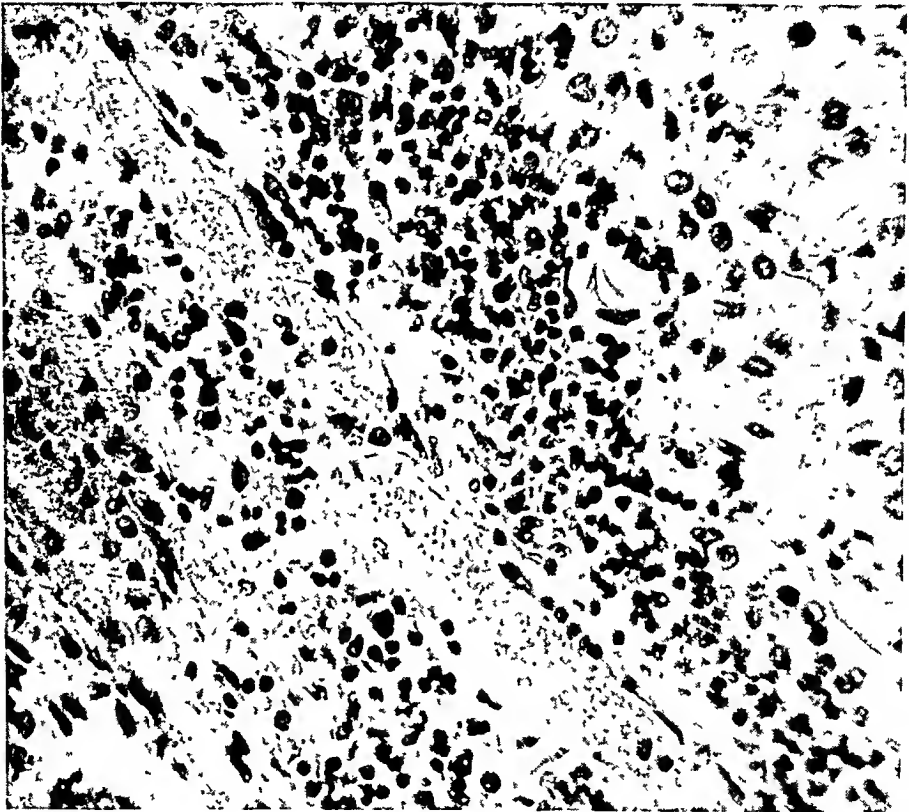


FIG 6 (Case 8) —Dilated vasa recti with dense perivascular infiltrations indicative of sulfonamide hypersensitivity in the right kidney occurring in a patient in whom renal insufficiency was initiated by shock. Aplastic left kidney. Death 9 days following partial esophagogastrectomy for carcinoma

surgical service and were selected for the availability of autopsy material and because the therapy which they had received for their renal insufficiency was in direct contrast to the management now advised.

Case 1.—C. J., age 36. Bronchiectases of the left lower lobe and lingula. Left lower lobectomy and lingulectomy 3/10/47. Prolonged hypotension despite repeated transfusions of whole blood (3000 cc). No untoward reaction to the transfusion was noted. The urine output in cubic centimeters on successive days was 0, 230, 60, 60, 0, 0, 30, 15, 240, 160, 120, 647, 807, 1043, 2000, 3000, 4500, 6200, 6925, 8115, 8075, 7000, 7200, 6656, 7200, 3700, 3275, 3125, etc. (See Figs. 1, 2, and Table II) During the entire course of his illness the patient was alert and cooperative. Subsequent hypoproteinemia and anemia were corrected with

concentrated serum albumin I.V. and transfusions of washed red cells and dietary measures. Vigorous replacement of salt losses during the period of diuresis was carried out. Despite a considerable weight loss, the patient recovered from the renal insufficiency (14 days) uneventfully and was discharged from the hospital feeling very well. Patient alive and well 1 year later.

**Case 2.**—W. S., age 64. Carcinoma of the stomach. Subtotal gastrectomy 2/6/48. Transfusion reaction with hemolytic jaundice, anuria (Fig. 3, Table II.) The patient received three transfusions during and following operation. Re-check of the original cross-match revealed no errors, both the recipient and 3 donors being typed A Rh =.

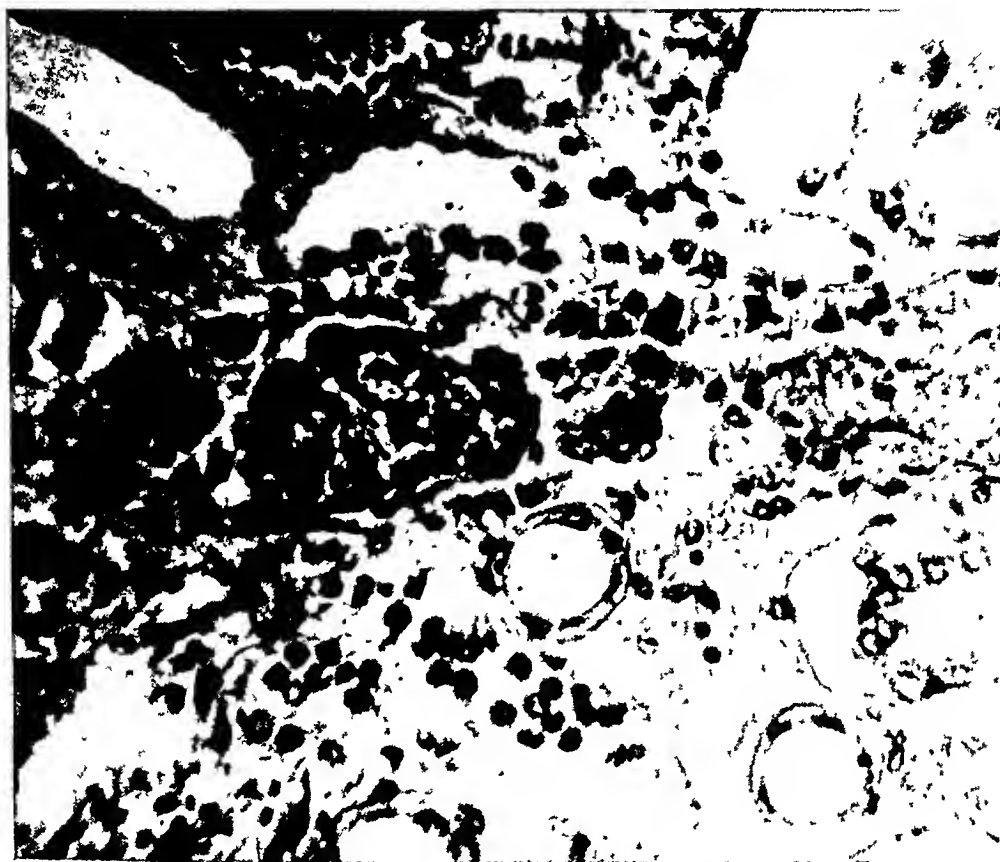


FIG. 7 (Case 6).—Granular heme casts in the distal portion of the nephron in a case of hemolytic transfusion reaction.

It was felt that the patient had been previously sensitized to a peculiar sub-group in the third donor. His history revealed that he had received both blood and plasma elsewhere. The first voided urine sample (P.O.) was port-wine in color and positive to both benzdine and guaiac. Urine output in cc.'s on successive days was 420, 16, 34, 50, 35, 52, 70, 160, 256, 705, 1065, 1815, 2445, 4100, 5200, 5325, 4250, 2150, etc. The patient remained alert, ambulatory and cooperative during the period of renal insufficiency (10 days) and recovered uneventfully.

**Case 3.**—E. H., age 64. Carcinoma of the urinary bladder. Cystectomy and bilateral uretero-sigmoidostomy 7/20/47. Hemolytic transfusion reaction with jaundice. Anuria. Hypertension and mild right hydronephrosis.

The patient was placed on a program of daily replacement of insensible loss of fluid—calculated at 1500 cc., periodic correction of the CO<sub>2</sub> combining power, calcium salts, 1 gram daily I.V., and replacement of salt loss. The urine output on successive days was 0, 0, 125, 75, 350, 450, 514, 655, 1470, etc. The blood NPN rose steadily to 296 mg.%

14 days after operation. The patient remained alert and cooperative during his entire illness and underwent a satisfactory recovery. Alive and well 4 months later. (See Table I.)

**Case 4.**—C. C., age 54. Essential hypertension. Bilateral splanchnicectomy and dorsal sympathectomy 1/8/48. Severe hypotension P.O. Anuria.

The patient's blood pressure fell to low levels in the immediate postoperative period and returned to normal only after vigorous supportive therapy. The urine output on successive days was 130, 150, 150, 850, 700, 710, 700, 1500, 1700, 2250, 2900, 2885, 2100, 3990, 3200, 2900, 2900, etc. During his entire illness the patient remained in a semi-stupor with periodic muscular twitchings which did not respond to any of various forms of therapy employed. These changes were believed to represent cerebral damage. Recovery from renal insufficiency began on the 8th P.O. day and it was felt that recovery would take place. On the 20th P.O. day, the patient experienced an episode of diarrhea with acute circulatory collapse and dehydration. This responded to parenteral therapy with salt solutions. Two days later, the patient expired from sudden cardiac decompensation. In retrospect, the possibility of hypopotassemia and insufficient salt replacement undoubtedly played a role in the sudden demise (Table II).

**Case 5.**—V.G., age 42. Carcinoma of the cervix grade IV-B with osseous metastases. Previous intensive irradiation therapy. Left nephrectomy, 1942, for calculous disease. Right hydronephrosis. Anuria from presumed sulfonamide sensitivity. Severe anemia.

For 24 hours prior to admission (2/28/48) the patient had been anuric. This was presumed to be due to ureteral obstruction. Cystoscopy and ureteral catheterization revealed an absence of urine both in the bladder and in the renal pelvis. Urine output on successive days was 0, 24, 275, 55, 50, 80, 1270, 1250, 1050, 1600, 1800, etc. In view of the positive fluid load on admission, fluid intake was restricted to an average of 1000 cc. daily for the first five days. The patient remained alert and cooperative and recovered from the renal insufficiency on a very conservative program.

**Case 6.**—F.S., age 41. Comminuted supracondylar fracture left humerus. Anuria following incompatible blood transfusion. (Donor A+, recipient O+.) Death nine days following transfusion reaction. Total intake 31,545 cc., total urine output 730 cc. during this period.

Autopsy revealed acute hemorrhagic parenchymatous nephritis (Fig. 7), multiple infarcts, emboli, petechial hemorrhages, intense pulmonary congestion and edema. Bilateral hydrothorax.

**Case 7.**—G. H., age 61. Chronic cholecystitis with lithiasis. Common duct stone. Obstructive jaundice. Liver abscess. Choledochoduodenostomy 4/15/43. Progressive renal insufficiency P.O. History of anuria in family from similar operation. Death six days P.O. Total intake 33,375 cc. Total urine output 1734 cc.

Autopsy revealed active ascending cholangitis, liver abscesses, bilateral hydrothorax, ascites, arteriosclerotic nephropathy and lower nephron nephrosis.

**Case 8.**—B.G., age 62. Adenocarcinoma cardia of the stomach with esophageal extension. Transthoracic esophago-gastrectomy 6/8/42. Prolonged P.O. hypotension (12 hours). Death 8 days following resection.

The patient received a total fluid intake of 38,835 cc. in the P.O. period. Total urine output, 9,130 cc.

Autopsy revealed an aplasia of the left kidney and lower nephron nephrosis of the right kidney (Fig. 6). (Sulfonamides had been administered in the P.O. period.) Pulmonary edema and atelectasis. Advanced arterio-sclerotic nephropathy.

**Case 9.**—R.V., age 30. Gas gangrene left leg. Amputation five days prior to admission. Disarticulation at knee and debridement of thigh 3/12/43. Death 3/16/43.

The patient was in deep shock on admission and remained moribund during his course in the hospital. Total intake (3 days) 12,175 cc. Urine output 665 cc.

Autopsy revealed lower nephron nephrosis and pulmonary edema with bilateral hydrothorax. Sulfa crystals were present in the renal tubules.

**Case 10.**—H.S., age 63. Far advanced carcinoma of the stomach with perforation and localized peritonitis. Multiple transfusion reactions (hyperthermia) and anuria. Gradual recovery renal function with urine output reaching 2600 cc. on 13th day. During this period patient was moribund from primary disease. Autopsy revealed lower nephron nephrosis (Fig. 4, 5) with advanced healing of tubular epithelium and crystals of undetermined etiology. Carcinoma of the stomach with perforation.

#### SUMMARY

A simple program of treatment for acute renal insufficiency of the lower nephron type is presented. The clinical course of the patients so treated has been entirely satisfactory.

It is conceivable that should renal tubular function fail to recover in the expected time interval, more energetic measures including hematodialysis should be employed. The authors have not found this necessary in the series of cases which they have treated.

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The authors wish to express their appreciation to Dr. A. J. French of the Department of Pathology, University of Michigan Medical School, for helpful assistance.

**DISCUSSION:**—DR. E. I. EVANS, Richmond, Va.: I am very sorry that because of the time limit Dr. Campbell did not get to present his complete material. We have learned from his and other work that one simply must not force the kidney to do work that it cannot do. In other words, we must let nature do what nature can do and, if nature cannot repair the damage, there is not much that one can do about tubular degeneration.

I rise only to point out that there is a preventive aspect in this, which I am sure he would have brought out had he had time. From all the work done on clinical shock during the past five or six years one thing has been learned, namely, if one is to prevent the shock kidney, one must keep to a very short period, the time the patient is in actual shock. One cannot take a long time to get infusions begun, one cannot expect good results in the therapy of shock when insufficient amounts of blood are given, and so on. There is a safe period of only about two or three hours at the most and if shock is prolonged beyond this period, tubular regeneration of the kidney cannot take place. We should not forget the important preventive aspect of this in considering the shock kidney.

DR. FREDERICK A. COLLIER, Ann Arbor (closing): Dr. Campbell has given you briefly a picture of the work of Trueta and his associates, Lucke, Mallory and others,

which I will not amplify except to express our indebtedness also to Muirhead and Hill. He has not had time to present to you in any detail the treatment of these patients with anuria associated with hypotension, tissue damage or blood incompatibilities. I will give an outline of the management of the two cases he has mentioned and shown on slides.

It can be divided into four phases: Phase I, in which the patient is or may be in hypotension. We agree with Dr. Evans that this should be corrected as soon as possible, otherwise the state may become irreversible. Transfusion of properly chosen blood is usually necessary. Phase II is that of oliguria or anuria. We have learned, as have others, that forcing fluid in the endeavor to force the kidney to work nearly always ends in disaster. Therefore, the patient is given only the amount of water that he is losing from his skin and lungs, which at comfortable environmental temperature is usually 1200 to 1500 cc. a day. This is given orally when possible, otherwise parenterally as 5 per cent glucose in water. The  $\text{CO}_2$  combining power should be followed daily and if it falls below 40, the impending acidosis must be corrected by the administration of sodium bicarbonate by mouth or sodium lactate solution intravenously. The patient is allowed to eat if he will do so; any light diet with low proteins seems satisfactory. If muscular twitchings develop, it will be found that the utilizable calcium is diminished, probably combining with phosphates, sulfates or bile salts in case of jaundice, and one gram of calcium glucosate is given each day. This program is carried out until diuresis occurs, which may not be for two or more weeks. The patients are comfortable and conscious if acidosis is not allowed to supervene in spite of the rising N.P.N. The third phase of the management covers the phase of diuresis. This must be watched for since it may come suddenly with the passage of several liters of urine. The water and salt must be replaced accurately and as lost. If this is not done, dehydration may cause death. Interestingly enough, the urine passed at this time is not concentrated, 1.010 to 1.014. The phase of diuresis may last two or three or more days, when the patient's condition improves and the urinary output approximates normal. The kidney does not return immediately to normal and we pass to Phase IV, in which the kidney recovers its former function, which may take a month or more. No special therapy is indicated. The high blood N.P.N. slowly declines. We feel that no special effort should be made to influence this chemical finding since other chemical abnormalities are more important.

We feel that not only should these patients be kept on the dry side, but that all patients who have had extensive traumatic operations, especially those that last many hours often associated with blood loss and hypotension, should also be given water with caution. The phrase "force fluids" should be abolished. It is nearly routine practice to start fluids with the operation and keep it flowing throughout the entire time of operation. The longer the operation the greater will be the trauma and the greater the chance for renal damage. The amount of fluid given should not be determined by the length of the operation, but upon other criteria. We have recently studied the management of water in patients undergoing combined abdominoperineal resection and in every instance there has been an adequate output of urine for 36 hours; that is, there has been water retention. The urine in this phase has the same characteristics as that passed by the post-anuric patient in the diuretic phase. Patients suffering from trauma, operative or otherwise, should be given fluids with great care. If water is given that cannot be utilized or excreted, harm may be done.

# THE SIGNIFICANCE OF URINE CHLORIDE DETERMINATION IN THE DETECTION AND TREATMENT OF DEHYDRATION WITH SALT DEPLETION\*

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WITH THE TECHNICAL ASSISTANCE OF

MISS RACHEL LEWIS AND MISS RUTH TAYLOR

FROM THE SURGICAL RESEARCH LABORATORY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA. THIS STUDY WAS CARRIED OUT UNDER A GRANT FROM THE OFFICE OF RESEARCH AND INVENTIONS, UNITED STATES NAVY.

THE PHYSICIAN FREQUENTLY faces the problem of how much and what kind of parenteral fluids to administer; in most cases the problem is the quantitative one of how much water and how much salt the patient needs. Neither physical examination nor estimation of plasma chloride concentration gives adequate information. However, our experiments with dehydrated human subjects indicate that, when renal or adrenal function is not damaged, the problem can be solved by measuring the urine volume excretion and urine chloride concentration, both of which are bedside determinations.\*

The physiologic principles of water and electrolyte balances, which have been developed especially by the work of Gamble<sup>2</sup> and Peters,<sup>3</sup> are well reviewed by Mariott.<sup>4</sup> Body water may be regarded as separated into three compartments: plasma, interstitial tissue fluid, and intracellular fluid (Fig. 1). Body electrolytes may be regarded as separated into two compartments: intracellular and extracellular, the latter corresponding to the plasma plus interstitial spaces (Fig. 2). Roughly speaking, the capillary membrane is freely permeable to water and electrolytes while the cell membrane is freely permeable to water alone. Equality of osmotic pressure throughout the body fluids, intra- and extracellular, is maintained by water shifts across all membranes and electrolyte shifts across the capillary membrane. The shifting extracellular electrolyte is predominantly sodium chloride (Fig. 2). Under ordinary conditions, the kidneys adjust excretion of water, and sodium chloride and other solids so accurately to intake that the volume and electrolyte concentration of the extracellular fluid are kept extraordinarily constant, providing the cells with the "internal environment" of Claude Bernard. For the cells to function normally, the volume of extracellular fluid must be kept adequate, and the

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\* By the method of Fantus,<sup>1</sup> urine chloride concentration can be quickly measured at the bedside with an accuracy of plus or minus 0.5 grams NaCl per liter of urine. The necessary apparatus and solutions are: a test tube, a medicine dropper, 20% potassium chromate, 2.9% silver nitrate, and distilled water for rinsing the dropper. To 10 drops of urine in a test tube, add 1 drop of potassium chromate solution and then silver nitrate solution, a drop at a time with shaking until the test tube contents suddenly change from yellow to brick red. The same dropper must be used throughout and rinsed between solutions. The number of silver nitrate drops required to produce the color change equals the urine sodium chloride concentration in grams per liter. Tests on 50 random hospital urine samples gave an average of 7.37 Gm. NaCl per liter urine with variations from 1 to 16 Gm. per liter.

\* Read before the American Surgical Association, May 27, 1948.

composition and pH must be kept within "physiological" limits; the osmotic pressure must be kept near that of 0.9% NaCl solution.

Local deviations from isotonicity are prevented by rapid water and salt shifts within the body; abnormal changes in the volume or composition of the total body fluids are prevented by the kidneys. When either water or salt intake is low or extra-renal loss is excessive, isotonicity is safeguarded by a corresponding decrease in either water or salt output by the kidneys. When renal mechanisms are normal one may expect to find small urine volumes with water depletion and low urine salt concentration and excretion with salt depletion. Such relationships are illustrated in the experiment presented below, and form the basis for the plan recommended for guiding parenteral fluid therapy.

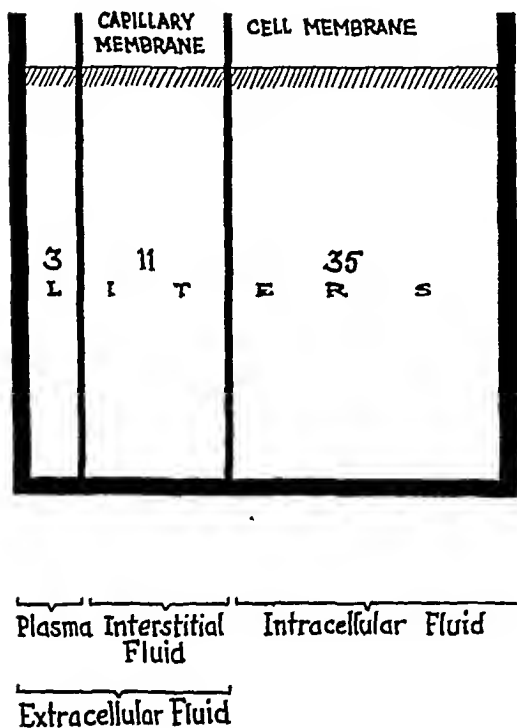


FIG. 1.—Body fluid compartments of normal 70 kg. man.

kidneys usually excrete enough salt to maintain extracellular isotonicity.

Primary salt depletion occurs when there is abnormal loss of salt from the body with adequate water intake. The salt loss may occur in profuse sweating, excessive vomiting, gastric suction, diarrhea or alimentary tract fistulae.\* Since the kidneys will not retain water without salt until the salt loss is severe, depletion of body water occurs, even if adequate amounts of water are drunk. Thus, though total body salt may be depleted, plasma chloride concentration

As Marriott points out,<sup>4</sup> dehydration is a term that covers two conditions that differ in cause, in physiologic and clinical effects, and in treatment needed. These conditions, named according to their initiating causes, are primary water depletion and primary salt depletion. (Marriott calls them "pure" depletion, but the term "pure" seems unfortunate, because salt deprivation or loss invokes accompanying water loss, and water deprivation or loss invokes salt loss.)

Primary water depletion is seen in conditions in which, usually because of generalized weakness or dysphagia, patients fail to drink adequate amounts of fluid. In debilitated patients it occurs more commonly than is recognized. The chloride concentration of the plasma may remain normal; the

\* The discussions and conclusions set forth in this writing do not pertain to the unusual electrolyte maladjustments encountered in Addison's disease.

may remain relatively normal so long as the extracellular fluid volume diminishes enough to compensate for the salt loss, and water excretion may remain adequate despite diminished extracellular fluid volume.

Figures 3 and 4 (taken from Marriott) show the theoretical water redistributions between the body compartments in primary water and primary salt depletion respectively.

With *primary water depletion* (Fig. 3) the extracellular fluid tends to become *hypertonic*, but this tendency is combated by two mechanisms; water moves across the cell membrane into the extracellular space, and the kidneys diminish their water output to the minimum obtainable by tubular reabsorp-

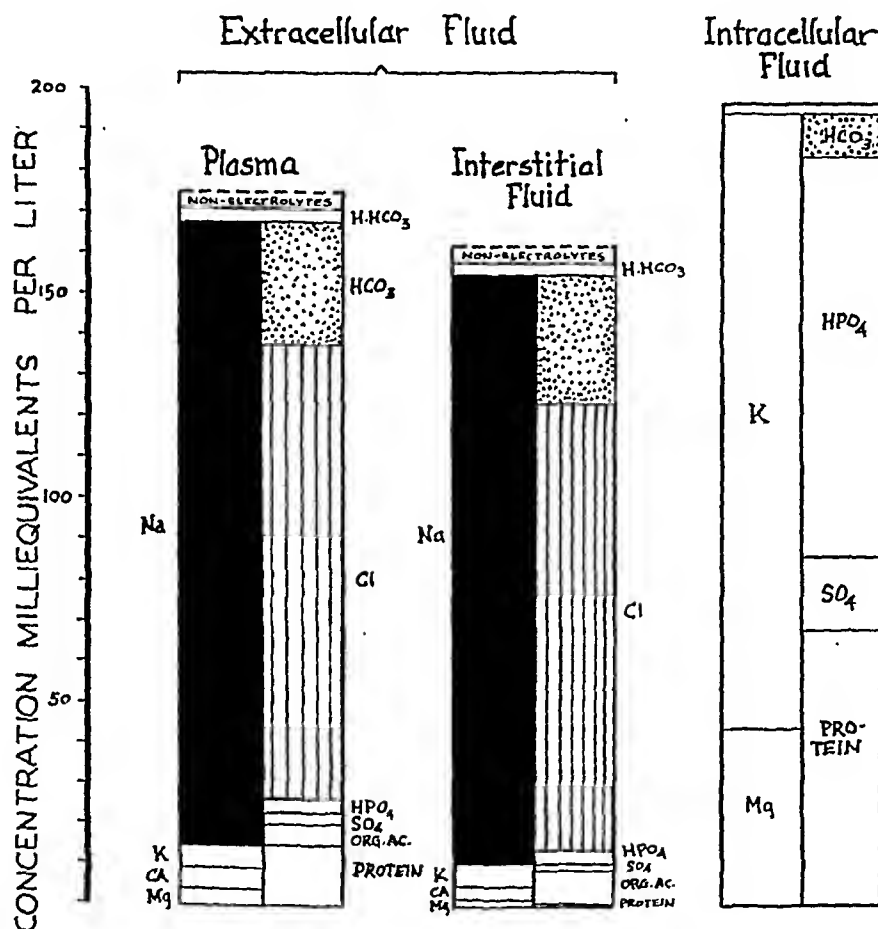


FIG. 2.—Composition of body fluid compartments of normal man.

tion. Although intracellular dehydration is marked, there may be no great change in either the plasma volume or electrolyte concentration. In this condition one may expect a *minimal urine volume*, normal or increased plasma and urine chloride concentrations, and no cardiovascular changes referable to diminished plasma volume.

With *primary salt depletion* (Fig. 4) the extracellular fluid tends to become *hypotonic*. The kidneys exert themselves to combat this tendency; *they continue to excrete water but practically no salt*. Plasma chloride concentration falls only when the kidneys can no longer excrete enough extracellular water to compensate for the salt loss. When plasma chloride con-



centration does fall, the loss of body water may be greatly out of proportion to the relative decrease in plasma chloride concentration. Shrinkage of plasma volume may become so great that clinical shock may develop.

In both primary water depletion and primary salt depletion, the kidneys exert maximum efforts to maintain isotonicity of the plasma and interstitial fluids, and in these efforts excrete urine that shows variations in volume and salt concentration greatly exceeding the variations in volume and salt concentration that occur in the plasma. The decrease of water excretion in pri-

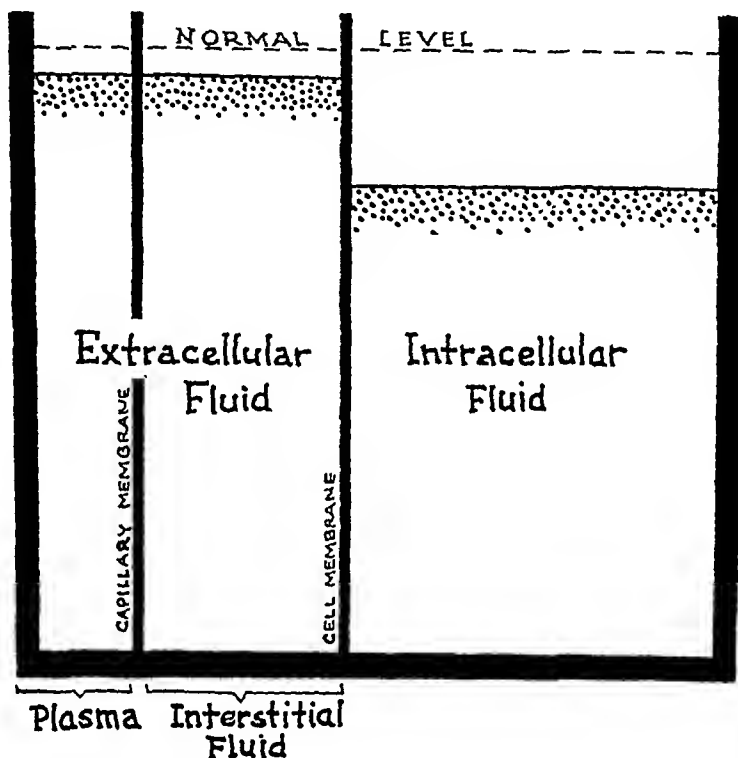
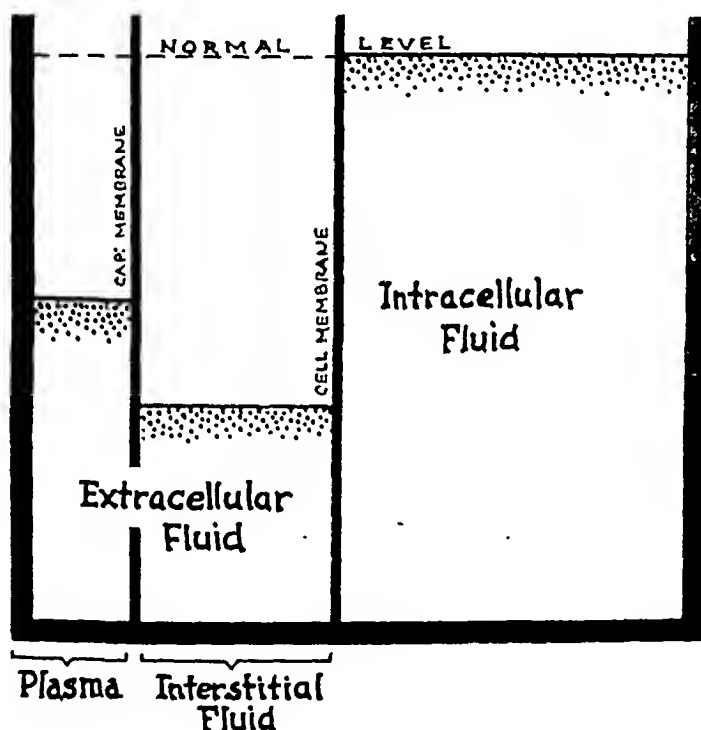


FIG. 3.—Water depletion.

mary water depletion, and of salt excretion in primary salt depletion, becomes marked when the plasma changes have hardly exceeded the normal range. Hence, it appears that, provided the kidneys are uninjured, urinary analyses can provide more sensitive indication of the occurrence and type of dehydration than can plasma analyses; that is, urine analyses can be expected to show earlier and more definitely than plasma analyses when body conditions change in either type of dehydration, from the normal to the abnormal.

On the other hand, since the kidneys respond early with nearly maximal limitation of water or salt output, it follows that urine analysis cannot be relied on to show the difference between moderate and severe dehydration of either type. The severity of the depletion may be determined either by observing the amount of water and salt therapy required to reestablish the excretion of water or salt, or by plasma measurements such as chloride and  $\text{CO}_2$  concentration, specific gravity and blood hematocrit.

When the kidneys are diseased, or injured by shock or severe dehydration, the urine probably does not indicate internal conditions of salt and water content as accurately as when the kidneys are normal. Even kidneys which have been apparently normal one day, may, as the result of a transitory period of shock, be so damaged that the next day they excrete only a small volume of urine with little solids of any kind. This may occur in the immediate post-



URINE CHLORIDE CONCENTRATION DECREASED  
PLASMA CHLORIDE CONCENTRATION NOT  
DECREASED UNTIL SALT DEPLETION IS  
GREAT

FIG. 4.—Salt depletion.

operative patient. Possibly salt retention postoperatively and during times of stress may result from the so-called "alarm reaction," a physiological state resulting from adrenal hormone secretion. Coller<sup>5</sup> and Moyer<sup>6</sup> have shown that postoperative patients tend to retain salt, and they have cautioned against overloading the patient with salt. Urine salt concentration or excretion cannot be used as a guide to salt therapy under conditions of renal salt retention. Further studies are needed to determine the conditions under which the kid-

## EXP. WL.

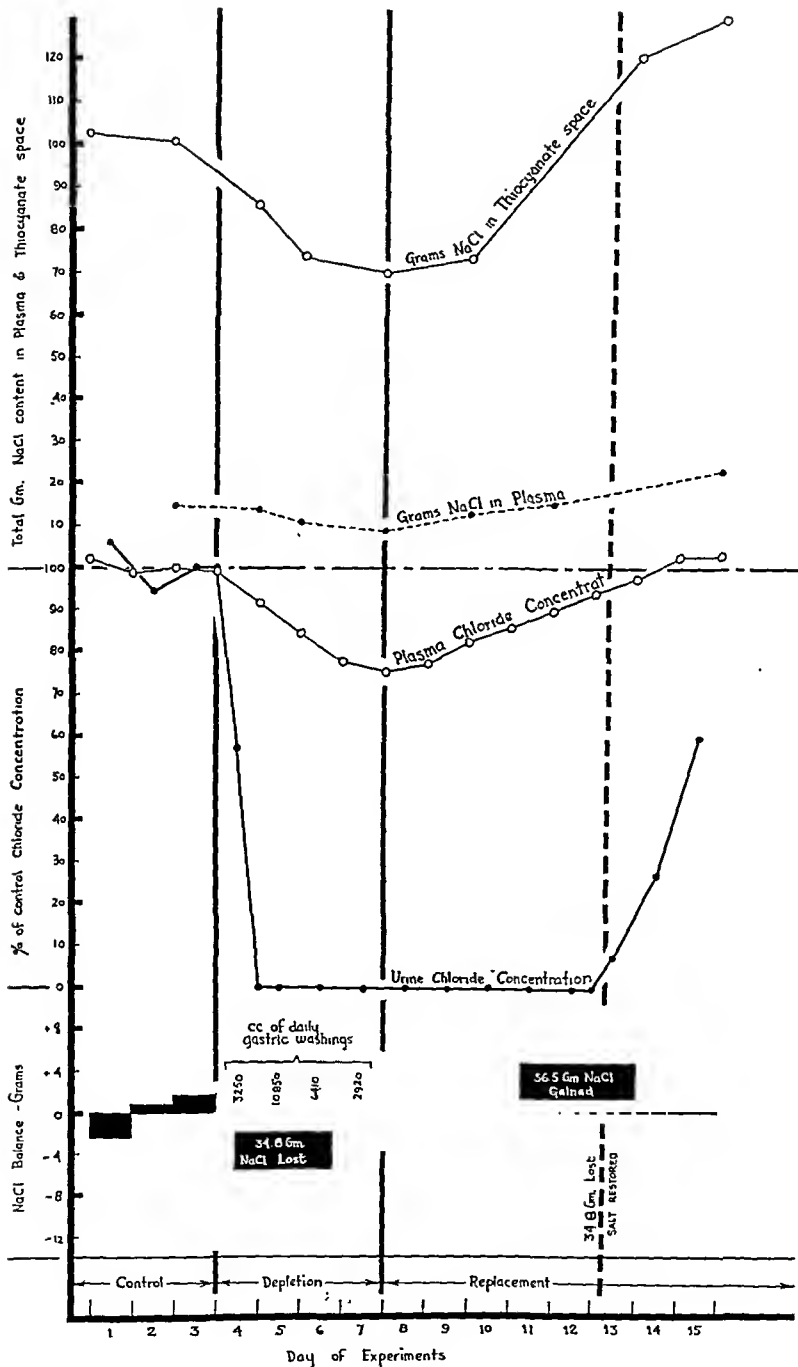


FIG. 5.—Human volunteer experimental demonstration of water and salt depletion showing: (1) the renal threshold level of about 95 percent normal plasma chloride concentration, (2) the greater sensitivity of urine chloride concentration as an index of salt depletion and replacement, (3) the excessive water and salt retention resulting from continued saline infusions after chlorides reappear in the urine.

neys do retain salt. Further studies are also needed to rule out the possibility of salt "spillage" into the urine during and following saline infusion. Such spillage could falsely indicate adequate salt replacement.

In the great majority of cases of dehydration encountered, however, urine analysis serves well to indicate early the occurrence and type of dehydration and to indicate when therapy is necessary or has been adequate to return the volume and salt content of the plasma and interstitial fluids to their normal ranges.

#### EXPERIMENTAL PROCEDURE

The following experiment, which is one of three, illustrates the applicability of the above principles in a case of mixed salt and water depletion caused by prolonged gastric suction.

W. L., a healthy medical student, voluntarily subjected himself to a carefully controlled 15-day water and salt balance study. This study (Fig. 5, Tables I, II, and III) may be divided into three periods: (1) Preliminary control—the first three days. Daily measurements were made during this control period and their average taken as "control." (2) Depletion period or period of gastric suction—the next four days. Constant gastric suction during this period produced a marked mixed water and salt depletion. Water was drunk as desired but was all recovered by gastric suction. No parenteral fluids were administered. (3) Replacement period—the last eight days. Water was drunk as desired. Salt depletion was slowly overcome by a measured dietary intake (0.8 to 1.2 Gm. NaCl daily), supplemented by intravenous 0.9% saline. The salt supply of the body was replaced slowly in order to increase the number of days over which the replacement could be observed. Five hundred cc. of 0.9% saline (4.5 Gm. NaCl) solution were given daily for three days, but since complete replacement appeared unlikely within the 15 days available for the experiment, daily 0.9% saline solution administration was increased to 750 cc. on the fourth day and to 1000 cc. the last four days. The experiment was ended when plasma chloride concentration no longer increased.

All chloride determinations were done in duplicate, using the open Carius method.<sup>7</sup> The salt intake was measured by chloride determinations of aliquot samples of diet and infusion solutions. Salt output was determined by measuring the volume and chloride concentration of 24-hour urine and gastric suction collections.

In order to compare urine and plasma chloride concentrations on the same chart, they are plotted as "per cent of control," the "control" values being the average of the control period concentrations.

The total salt content of the plasma was measured by multiplying the plasma salt concentration (calculated from chloride) times the plasma volume, the latter being measured with T-1824 blue dye.<sup>8</sup> Total extracellular space salt content was estimated by multiplying the plasma salt concentration by the thiocyanate space volume.<sup>8</sup> Both plasma volume and thiocyanate space determinations were made from six-point disappearance curves using a Coleman Model 6 spectrophotometer.

TABLE I.—*Experiment W. L.—Daily Salt Balance*

Experimental Period	Day of Experiment	NaCl Intake (Gm.)			Gastric NaCl Output			Urine NaCl Output			NaCl Out-put (Gastric Plus Urine)	NaCl Balance (Intake Minus Output)
		Diet	Tablets	Intra-venous NaCl	Wash-ings cc./day	Concen-tration (Gm./L)	Total Gm. NaCl/day	cc./day	Concen-tration (Gm./L)	Total Gm. NaCl/day		
Control.....	1	0.84	5	0	—	—	—	2,210	3.7	8.2	8.2	— 2.4
	2	0.87	3	0	—	—	—	975	3.3	3.2	3.2	+ 0.7
	3	1.17	3	0	—	—	—	735	3.5	2.6	2.6	+ 1.6
Depletion.....	4	0	0	0	3,250	3.34	10.9	735	2.0	1.5	12.4	— 12.4
	5	0	0	0	10,850	1.25	13.5	490	0	0	13.5	— 13.5
	6	0	0	0	6,410	0.92	5.9	425	0	0	5.9	— 5.9
	7	0	0	0	2,900	0.96	2.8	605	0	0	2.8	— 2.8
Replacement.....	8	0.49	0	4.5	—	—	—	1,170	0	0	0	+ 5.1
	9	0.63	0	4.5	—	—	—	2,140	0	0	0	+ 5.0
	10	0.87	0	4.5	—	—	—	2,495	0	0	0	+ 5.4
	11	1.20	0	6.8	—	—	—	1,990	0	0	0	+ 8.0
	12	0.84	0	9.0	—	—	—	1,980	0	0	0	+ 9.8
	13	0.87	0	9.0	—	—	—	1,240	0.3	1.3	0.3	— 9.6
	14	1.20	0	9.0	—	—	—	1,910	1.8	1.8	1.8	+ 8.4
	15	0.87	0	9.0	—	—	—	2,270	4.7	4.7	4.7	— 5.2

Hematocrits were measured in quadruplicate by centrifugation at 3000 RPM for 45 minutes. Plasma total protein concentrations were determined by the copper sulfate specific gravity method of Phillips, et al.<sup>9</sup>

Other measurements were: body weight, urine pH, urine specific gravity, urine CO<sub>2</sub>, plasma CO<sub>2</sub>, and plasma total base concentration. The measurements pertaining to acid-base balance will be presented in a subsequent publication.

All measurements were made daily except plasma volume and thiocyanate space. These were measured about every other day.

#### EXPERIMENTAL RESULTS

Examination of Figure 5 and Table I, II, and III show that the subject was in good salt balance during the preliminary control period; plasma chloride concentration varied  $\pm 2\%$ , urine chloride  $\pm 6$ ; total extracellular salt estimations were 103 and 101 Gm.

TABLE II.—*Experiment W. L.—Chloride Measurement*

Experi- mental Period	Day of Experi- ment	Plasma Chloride Concentration			*Total Plasma NaCl Content (Gm./ NaCl)	†Total Thio- cyanate Space NaCl Content (Gm./ NaCl)	—Urine NaCl—	
		(mEq/L)	(mg % NaCl)	% Control			Concen- tration (Gm./L)	% Control Concen- tration
Control.....	1	106.0	620	ave. =		102.9	3.7	ave. =
	2	102.4	599	100%	—	—	3.3	100%
	3	103.8	607		15.5	101.0	3.5	
Depletion.....	4	103.4	605	100.0	—	—	2.0	57
	5	97.6	571	94.2	14.0	86.2	0	0
	6	88.6	518	85.5	11.0	73.0	0	0
	7	81.2	475	78.4	—	—	0	0
Replacement...	8	78.4	459	75.7	9.0	69.8	0	0
	9	80.4	470	77.6	—	—	0	0
	10	86.2	509	83.2	12.5	73.8	0	0
	11	89.6	524	86.5	—	—	0	0
	12	93.6	548	90.3	15.6	—	0	0
	13	98.0	573	94.6	—	—	0.3	0.7
	14	101.6	594	98.1	—	120.6	1.0	27
	15	107.0	626	103.3	—	—	2.1	60
	16	107.4	628	103.7	23.2	130.6	—	—

\* Total plasma salt content = plasma NaCl concentration  $\times$  plasma volume

† Total thiocyanate salt content = plasma NaCl concentration  $\times$  thiocyanate space volume.

During the four days of gastric suction there was a daily negative salt balance of  $-12.4$  Gm.,  $-13.7$  Gm.,  $-5.9$  Gm., and  $-2.8$  Gm.; a total of 34.8 Gm. of salt loss in four days. Salt replacement was completed on the sixth day of the replacement period, 33.2 Gm. NaCl having been replaced at the end of the fifth day and a total of 43.1 Gm. by the end of the sixth. The positive salt balance during the final three days represents a retention in excess of that lost during the depletion period.

During the first day of gastric suction, extracellular salt content decreased 15 Gm., a loss equal to the total amount of salt normally present in this subject's plasma. Despite this salt depletion, plasma chloride concentration fell

only 6%, while on the other hand, urine chloride concentration fell to zero and remained zero. These figures show that the moderately severe salt depletion was quickly apparent from the decrease in urine chloride concentration while it was scarcely detectable from the plasma chloride concentration determinations. The plasma chloride concentration was being maintained by cessation of chloride excretion in the urine.

At the end of the depletion period, plasma chloride concentration was 459 mg. %, a fall of only 24% below normal control concentration. At this time the extracellular salt content had fallen 32 Gm. below normal, this figure checking well with the 34.8 Gm. of NaCl recovered from the gastric fluid and

TABLE III.—*Experiment W. L.—Miscellaneous Data*

Experi- mental Period	Day of Experi- ment	Body Weight (Kg.)	Spun Hemat- ocrit, Percent	Total Blood Loss by Vena- puncture (cc.)	Total Plasma Protein (Gm. %) Gm./ cc.	Plasma Volume (cc.)	Thio- cyanate Space (cc.)	Urine Sp. Gr.
Control.....	1	63.20	45.0	50	6.29	—	16,600	1.009
	2	62.50	48.5	62	6.69	—	—	1.004
	3	63.15	45.4	112	6.29	2,560	16,600	1.020
Depletion.....	4	53.00	44.5	124	6.30	—	—	1.014
	5	59.10	48.0	174	7.35	2,460	15,100	1.031
	6	57.50	51.4	224	—	2,120	—	1.027
	7	57.10	54.1	236	8.60	—	—	1.022
Replacement.....	8	56.55	52.5	286	7.26	1,950	15,200	1.019
	9	57.40	—	298	7.36	—	—	1.009
	10	58.90	41.7	348	6.65	2,460	14,500	1.007
	11	58.20	41.8	360	6.28	—	—	1.008
	12	59.40	39.4	410	6.22	2,850	9,800	1.007
	13	59.75	37.8	422	5.74	—	—	1.013
	14	60.45	33.6	472	5.03	—	20,300	1.008
	15	61.00	34.0	484	5.03	—	—	1.008
	16	61.50	33.4	534	5.03	3,700	20,800	—

NB—The following daily observations will also be reported in a future publication;  
Plasma CO<sub>2</sub>, plasma total base, urine pH and urine CO<sub>2</sub>

urine, and corresponding to one-third of the normal extracellular salt content, and twice the normal plasma salt content. This fall in plasma chloride concentration indicated a serious alteration in extracellular isotonicity. Clinically, the subject was lethargic, fainted on rising from bed, his eyes appeared sunken, the skin became loose and dry and scaly. Despite this extreme water and salt depletion, the plasma chloride concentration never fell as low as had the urine chloride concentration during even the first day of depletion.

The fall in urine volume to a minimum of 425 cc. per day would be expected in this state of "mixed" water and salt depletion. Reduction in both urine volume and urine chloride concentration indicate a mixed depletion requiring both salt and water therapy.

During the third part of this experiment, water was restored by free oral intake while salt restoration was accomplished by a low salt diet supplemented

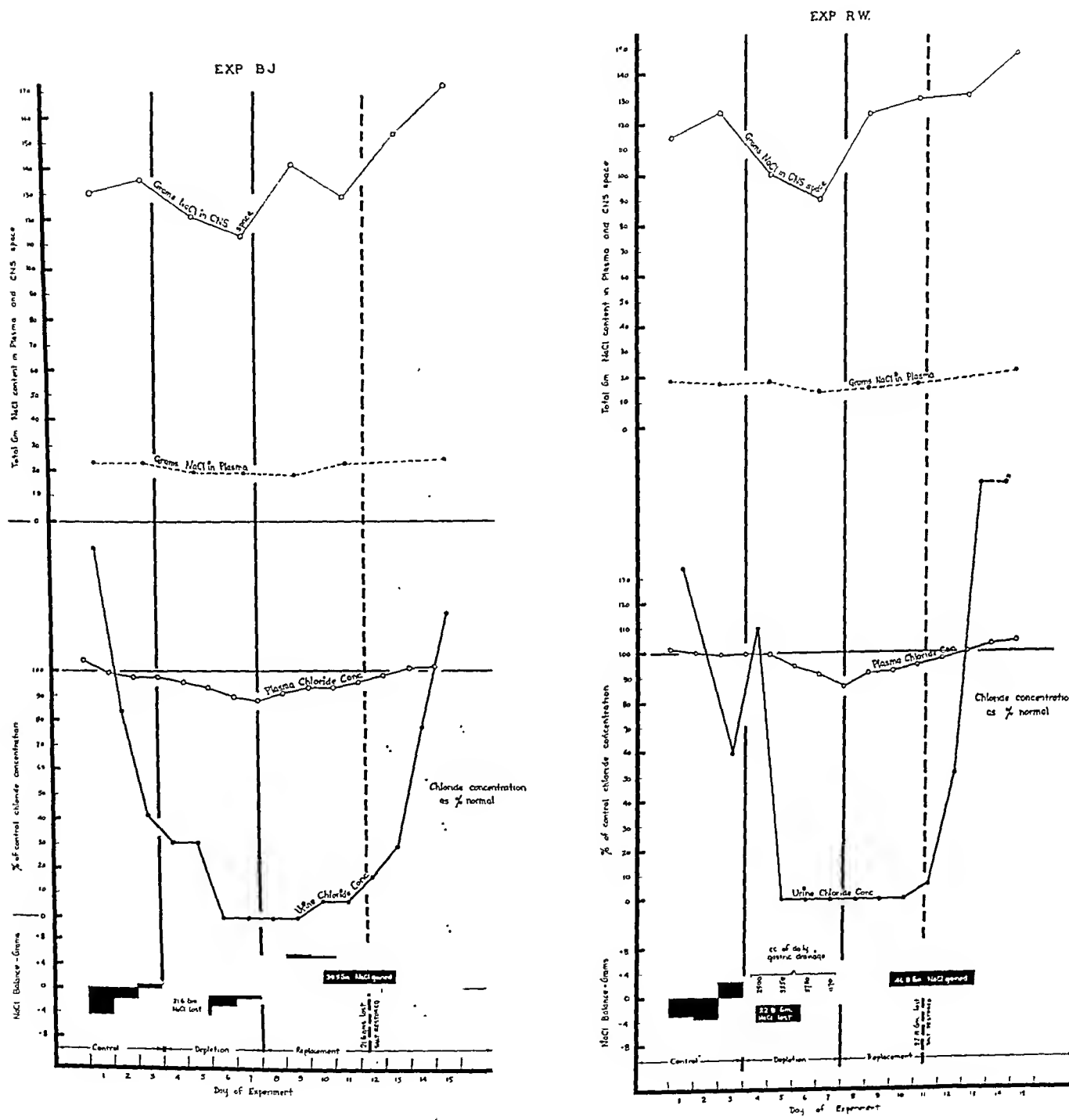


FIG. 6.—Showing experiments identical to that of Figure 5. The results are confirmatory.



by intravenous 0.9% saline. Salt replacement was completed during the early part of the sixth day. At this time (see vertical broken line on Fig. 5) the extracellular and plasma salt contents had returned to normal, chloride reappeared in the urine, but plasma chloride concentration had returned to only about 95% normal. Continuation of daily infusions of 1000 cc. 0.9% saline during the final four days caused a rapid increase in extracellular salt content and urine chloride concentration, and by the time plasma chloride concentration returned to normal, the total number of grams of salt in the extracellular fluid was 120% of the amount observed in the preliminary control period.\* That this actually represents a subclinical edema is confirmed by the hematocrit and total protein concentrations; both fell to 20% below normal (corrected for experimental red blood cell and protein loss). Apparently urine chloride concentration better indicated salt replacement than did plasma chloride concentration; for chloride reappeared in the urine as soon as the 34.8 Gm. body salt deficiency was replaced, while return of plasma chloride concentration to normal was accompanied by overloading of the extracellular space with salt and water.

This experiment indicates a renal threshold level of about 95% normal plasma chloride concentration. Below this concentration chloride did not appear in the urine. It supports the physiologic hypothesis presented earlier in this paper and demonstrates the advantages of urinary over plasma chloride analysis.

Figure 6 represents similar studies carried out on the two other volunteer subjects. The results are similar to those discussed above. There was a renal threshold level of about 95% normal plasma chloride concentration. Below this level, chloride did not appear in the urine. The urine chloride concentration was a much more sensitive indicator of salt depletion and replacement than was the plasma chloride concentration. Continuation of saline infusions after chloride appeared in the urine caused excess salt and water to be retained in the extracellular space.

#### DISCUSSION

A slight discrepancy between the experimental observations published here and those reported earlier from this laboratory<sup>10</sup> is to be noted. It was observed in dogs that "When a condition of salt depletion is being established, drop of chloride excretion to a low rate is a more sensitive indicator of the condition than is the plasma chloride concentration. But when the condition of depletion of the type caused by loss of gastric juice is in process of correction by NaCl administration, restoration of normal plasma chloride concen-

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\* The changing thiocyanate space volume in this experiment is not a cumulative technical error resulting from accumulation of repeated thiocyanate dosage. This was proven by repeating the series of thiocyanate determinations in this same subject while in a normal state six months after the experimental period. Thiocyanate space measurements every other day for two weeks gave the following volumes: 15.5L, 15.0L, 18.2L, 17.9L, 17.3L, 16.3L, 17.4L, 17.9L.

tration shows more accurately than resumption of chloride excretion when enough saline has been given to correct the condition." During salt replacement there was a lowered renal chloride threshold in the dog experiments, but this was not observed in the experiments on man.

This discrepancy is best explained by the great difference in experimental conditions. In the dog experiment reported, salt replacement was conducted rapidly, i.e., 1 Gm. NaCl per pound body weight during 12 hours, and there was a diuresis of the accompanying dextrose and water infused. A single massive intravenous infusion was given. Salt replacement in the human experiment was accomplished slowly over five to six days, no rapid infusions were given, nor was diuresis stimulated.

The present work does confirm the previous observations<sup>10</sup> that an internal alkalosis resulting from hypochloremia may be accompanied by the excretion of an acid urine. Such a paradoxical concurrence was invariably present in the present experiment. Measurements of urinary pH, urinary CO<sub>2</sub>, plasma CO<sub>2</sub>, and plasma total base concentration of this and other subjects will be reported in the future.

#### CONCLUSIONS

There is sufficient evidence both in the literature (11, 12, 13, 14, 15, 16) and in our experiments on human volunteers to justify suggesting that, providing kidney and adrenal function are normal, *water and salt balance will be properly maintained if daily urine volume exceeds 1500 cc. and urine salt concentration approximates 3 Gm. per liter.* Since urine volume and approximate salt concentration are simple bedside determinations, they have been found very useful as routine guides to parenteral water and salt administration. It is fortunate that these guides are at the same time most informative and simple to determine, and are thus admirably adapted to clinical use.

There is a discrepancy between the above conclusions and the data presented in Figure 5. Figure 5 shows that chloride reappears in the urine as soon as salt restoration is complete (vertical broken line) and that increasing urine salt concentration is accompanied by excessive water and salt retention. This observation is confirmed in the other experimental subjects. Despite this experimental observation, it is recommended that salt balance will be best maintained if urine salt concentration is maintained at about 3 Gm. NaCl per liter. Limited clinical observations suggest that salt deficiency is apt to occur if one attempts to keep urine salt concentration slightly above zero; it has been easier and safer to maintain about 3 Gm. per liter urinary salt. Clinical studies of Bartlett et al<sup>11</sup> are in agreement with the experimental findings presented here. They recommended that, when their "volume for volume" rule cannot be followed, urinary chloride excretion be maintained at one or less grams per day, although such procedure may result in slight chloride depletion and fall in plasma chloride concentration. On the other hand, Hadden<sup>12, 15</sup> recommends that saline infusions be given until the urine contains 5-10 Gm. of NaCl in 24 hours. Saucedo-Vegas and Collins<sup>14</sup> agree with Hadden. Those recommending minimum urinary salt excretion do so in

fear of salt retention, while those recommending relatively great salt excretion fear salt depletion. A compromise seems advisable and agrees with the recommendation that urinary salt concentration be kept at about 3 Gm. per liter and urinary output at about 1500 cc. per day. Further clinical observations will decide whether these recommendations are optimum.

Urine salt concentration rather than daily salt excretion is recommended with the realization that the latter is probably a more accurate guide to salt administration. However, the determination of daily salt excretion necessitates the inconvenience of measuring the salt concentration of aliquot samples of twenty-four-hour urine collections. Furthermore, it is convenient to measure the urine salt concentration at the bedside just before starting each infusion, and to administer dextrose solution if there is more than 3 Gm. of salt per liter of urine, or saline solution if there is less than 3 Gm. per liter.

It is also suggested that urine salt concentration determination may be used to detect the presence or absence of body salt depletion. If the Fantus test is used and one drop of silver nitrate turns the urine-potassium chromate mixture red, one may assume that salt depletion is present; and, conversely, when there are at least 3 Gm. of salt per liter of urine, saline therapy is rarely indicated.

Thus the information obtained from urine NaCl concentration measurement at the bedside or in the emergency room is valuable in deciding whether or not the patient needs salt therapy, while measurement of urine volume excretion is valuable in deciding whether or not the patient needs water therapy. We must not place complete dependence on these simple measurements as quantitative guides to such a complicated physiological mechanism as water and salt equilibrium. These guides must be supplemented by clinical observations of edema, skin turgor, thirst, respiration, the appearance of the tongue and eyeballs, mental state, etc.

It is not suggested that plasma chloride determinations be discarded. As salt depletion progresses, salt first disappears from the urine and then plasma chloride concentration continues to fall. Once the urine has become salt free, plasma chloride concentration must be determined in order to estimate the magnitude of salt depletion. If plasma chloride concentration is abnormally low, plasma CO<sub>2</sub> concentration must be measured.

In the presence of decreased kidney function it is probably safer to depend on plasma chloride than on urine salt measurements; poorly functioning kidneys may fail readily to excrete salt. There is evidence indicating that renal function may be depressed in conditions causing diminished blood volume, as in dehydration, during and immediately following shock, and immediately postoperatively. Further studies are needed before urinary salt determinations can be recommended in these conditions.

At present there is discussion in the literature concerning the concentration of saline to be infused intravenously. Further discussion is intentionally avoided here, for it is the purpose of this paper to separate dehydration into two categories, water depletion and salt depletion, and to recommend that

each type of depletion be treated separately. Discussion of electrolytes other than NaCl is also avoided in this paper, although it is understood that simple NaCl therapy is frequently incomplete electrolyte therapy.

#### SUMMARY

It is suggested that the loose term "dehydration" be substituted by its physiologic components: "primary water depletion," "primary salt depletion," and "mixed water and salt depletion." The physiologic basis for this recommendation is presented as well as the reasons for using urine salt (measured as chloride) concentration and urine volume instead of plasma chloride concentration as a guide to the diagnosis and treatment of these various types of dehydration. An experimental study of volunteer subjects is presented in support of this recommendation.

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DISCUSSION.—DR. I. S. RAVDIN, Philadelphia: These studies represent the type of work which is necessary to provide a clearer knowledge of the fluid and electrolyte requirements of surgical patients. In adopting Marriott's classification which divides dehydration into two conditions that differ in cause in physiologic and chemical effects,

and in the treatment needed, they have provided a more rational concept of the problem of dehydration and they have further strengthened our thinking by calling these conditions "primary water depletion" and "primary salt depletion." Anyone who has attempted to study the shifts in fluids and electrolytes in man, in health and in disease, knows that most of the methods now being utilized provide meagre data on what is happening in the body as a whole, and in the specific compartments which go to make up the whole. The part which the normal kidneys play in their effort to maintain isotonicity of the plasma and interstitial fluids was stressed some years ago by James Gamble and his associates. It should be recognized that urinary analyses such as Dr. Evans and Dr. Van Slyke are making are particularly useful when the kidneys are normal. The conditions initiating primary water and/or salt depletion, however, frequently result in a variable degree of renal injury, as Dr. Campbell and Dr. Collier and their associates have shown. Under such conditions, the authors have rightly pointed out that the urine may not correctly indicate the internal conditions of salt and water content. In the seriously ill surgical patient, abnormalities in glomerular infiltration, tubular secretion and absorption, exist all too frequently. It is in these patients that the excretion of an apparently normal urinary volume may be associated with marked abnormality in base, chloride and other electrolyte excretions. Under such circumstances it may be far better to be very cautious in the administration of large amounts of fluid or salts, as Dr. Collier pointed out in his discussion. This is especially true in nephrosclerosis or in kidneys subjected to periods of anoxia. It may be better to keep the patient in a state of mild hypochloremia than to risk the untoward effects of the burden which the opposite state may impose on the patient.

There remains much to be learned about the function of the kidneys in health and in disease, of the effect of the different renal components on various salts and especially such salts as potassium salts and calcium salts. In certain conditions there is generalized renal impairment, but tubular and glomerular dysfunction are not necessarily impaired to the same degree. The entire picture may be further complicated by abnormalities in plasma protein; for in severe hypoproteinemia there is apt to be specific sodium retention. Studies of the type reported in the last two papers facilitate greatly our thinking upon the problems of renal and will, we hope, provide a more rational basis for parenteral fluid and salt therapy in surgical patients.

DR. JOHN H. GIBBON, JR., Philadelphia: I think Dr. Collier's warning that patients with anuria should be kept on the "dry side," merely replacing insensible water loss, is a very important one. Kolff of Holland, who developed an apparatus for the dialysis of blood outside the body, is in hearty agreement with this point of view. These patients will often recover provided they are not drowned by excessive amounts of intravenous fluid and provided the acid base equilibrium is maintained. I think the observation on the great loss of salt and water which occurs during the period of diuresis, is very interesting.

Drs. Evans and Van Slyke are to be congratulated on a beautiful piece of work in carrying out experiments on normal human subjects and presenting us with a very practical test for determining what we all want to know at the bedside, i.e., whether we should give a patient salt solution, or glucose and distilled water, intravenously.

DR. KENNETH N. CAMPBELL, Ann Arbor: This paper brought out extremely important factors which Dr. Van Slyke did not have time to emphasize. The first of these is the fallacy of basing therapy on a laboratory value. May I give very concrete examples: I speak particularly of laboratory values for plasma chloride. If we take the normal plasma volume at 3000 cc., and order a plasma protein determination from the laboratory that comes back some 7 Gr. per cent, that would give us a total circulating protein in our plasma of some 210 Gm. Now, if perchance that individual did not have a normal plasma volume, let us say he had been subjected to dehydration or to plasma loss from some other cause, we might receive back from

the laboratory a plasma protein value of eight grams per cent at a time when the plasma volume was not 3000 cc. but 2000 cc. With simple arithmetic that will tell you that we now have only 160 Gm. of total circulating protein and not 210. Our laboratory value is higher, it is better than the example I gave you previously, and may lead one very erroneously into assuming that that patient has a normal total circulating protein. Similar changes may occur obviously in determinations of chlorides.

We are very happy to hear of the experimental work that Drs. Evans and Van Slyke have reported concerning the interpretation of plasma chloride values. They have simplified it to its utmost on a rational basis.

I will finish by saying something about volume for volume replacement which we have heard so much about in the past. If one institutes gastric or intestinal drainage and replaces volume for volume the secretions obtained with the solutions we now have available, and we call those normal physiologic solutions—when they are not either normal nor physiologic—you may be replacing approximately twice the amount of salt that you are withdrawing from your intestinal or gastric drainage.

DR. E. I. EVANS, Richmond, Va. (closing): We should like first to thank Dr. Ravdin for his comment. I should like then to say that I was much impressed by the remarks made by our President this morning about teaching surgery to medical students. I refer to this now because of what we have learned by placing in the hands of the medical student this simple bedside urine chloride technic, so that they may follow their patients day by day and learn thereby the fundamentals of fluid balance and salt therapy. We get almost every week requests from new groups of students on the ward for these little laboratory beside kits so that they can run urine chlorides on their own patients. It is gratifying for a teacher to learn how easy it is to get a little idea across once a year or so.

Third, I am happy that Dr. Lockwood brought up the important point potassium deserves in his reference to Dr. Darrow's work. It is rather interesting in observing cycles of surgical research how often different groups become interested in the same type of thing at about the same time. We are following with interest what Dr. Lockwood's group is doing. We have come to similar conclusions and have learned a great deal from Dr. Darrow's presentations.

It is well here to call attention to the extreme danger of giving adrenal cortical hormone to those surgical patients who are suffering from hypochloremic alkalosis. We have learned that one cannot correct this alkalosis by administration of salt or Ringer solutions if at the same time one is administering even small amounts of adrenal cortical hormone.

About the "dry" side. We agree, Dr. Campbell, with everything you say, but I cannot sit down without emphasizing again, be "dry" on the side of sodium chloride or water, but don't be "dry" on the side of whole blood when it is needed.

## STRESS, STRAIN AND SUTURES\*

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TWO BRIDGES ARE ILLUSTRATED in Figure 1: One is constructed without definite knowledge of the strength of component parts and without consideration of the load to which it may be subjected; the other, in contrast, is a product of engineering skill and art in which the strength of every bolt and cable, strut, beam and column is known, where each structural part is adjusted to meet calculated stresses and strains with ample margins of safety. What will happen to the toy bridge when Junior steps on it is anybody's guess, but the safety of the engineer's bridge is no guesswork; every day thousands of people unhesitatingly entrust their lives to it.

In operative surgery there are also potentially dangerous stresses and strains and practical problems of mechanical forces. It is often literally true that the life of a patient hangs by a thread.

The tensile strength of sutures, in the strand and at the knot, depends upon the size of the thread and the material of which it is composed. (Fig. 2). Given the same material, tensile strength varies with the square of the diameter of the thread; double the diameter and you quadruple the strength. Knot breaking strength, as a rule, is about 70 per cent of the tensile strength of the strand away from the knot. Brittle material like silkworm gut is relatively weak at the knot. Size for size, the weakest suture material is wet catgut. This material is distinctive also in that, after implantation in tissues, it rapidly loses what strength it has.

Table I shows how badly is needed a uniform gage for all suture material. A gage, based, let us say, upon thousandths of an inch diameter would enable the surgeon, by quick reference to an appropriate chart, to determine the tensile and knot-breaking strength of any given thread, and to suit the sort and size of sutures to his immediate purposes.

The strength of sutures depends not alone upon the tensile strength of the strand, but also upon the security of the knot. Each of the horizontal stripes in Figure 3 represents a set of 20 tests. None of the five commonly used knots represented there is safe when the ends are cut very short; indeed, the only dependable knots are those with three throws, the ends being cut 2 or more mm. long. Similar results are obtained with cotton (Fig. 4); nor is the pattern of these tests altered significantly by wetting the thread with water or serum, by waxing or oiling the thread, or by using boiled or autoclaved thread. Results with catgut are much the same (Fig. 5). Steel wire knots are very prone to slip. Particularly unreliable are those knots which tighten down when the second throw is pressed home, and the knot which ends-off a continuous suture, in which two strands are tied to one.

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\* Read before the American Surgical Association, May 27, 1948, Quebec, Canada.

TABLE I.

COMPARATIVE SIZE (DIAMETER) OF SUTURE MATERIAL

Diameter in inches	CATGUT		SILK		NYLON		COTTON		WIRE	
	Dry	Wet	Surgical	Commercial	Surgical	Commercial	Surgical	Commercial	Tantalum	Steel
28		No. 1								No. 22
26										
25	No. 2		No. 2							
24		No. 0								
23					No. 3					
22	No. 1				No. 2					No. 24
21										
20			No. 1							
19	No. 0	No. 00								
18										No. 26
17							"C"			
16	No. 00							"8"		
15			No. 0					"10"		
14		No. 000								No. 28
13					No. 00		"E"	"20"		
12	No. 000							"30"		No. 30
11		No. 4-0					"A"			
10			No. 000		No. 000		No. 0	"40"		
9	No. 4-0	No. 5-0						"50"		No. 32
8	No. 5-0		No. 4-0	"A"	"A"			"60"		
7							No. 000	"80"		No. 34
6			No. 5-0							
5									CO5 1/2"	No. 35
4			No. 6-0							No. 36
3									CO3 1/2"	

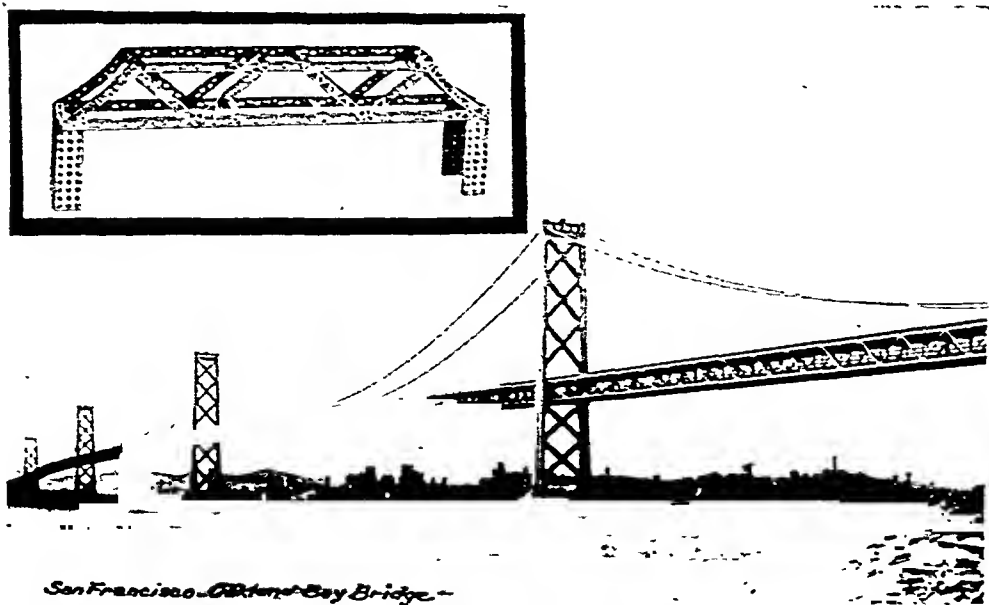


FIG. 1.—A splendid example of engineering skill, contrasted with a toy bridge (inset) which is constructed without regard to principles of engineering.



*Tensile Strength of Suture Material*

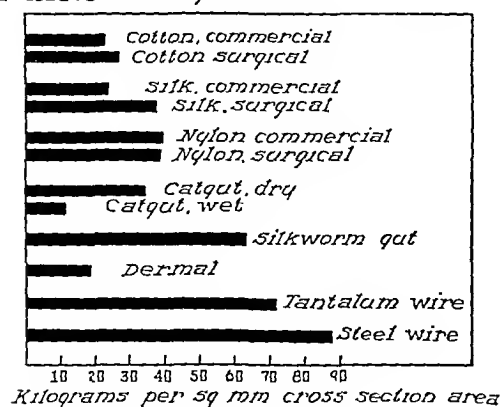


FIG. 2.—Relative tensile strengths of suture materials.

Actually in surgery we deal with loops rather than straight strands. The strength of a simple loop is double that of a straight strand (Fig. 6), and a double loop is four times as strong, presumably because of distribution of tension and friction against the tissues.

In surgery, loops are subject not only to the longitudinal pull indicated in Figure 6, but also to intraloop tensions. For example, a ligature placed around an artery (Fig. 7A) must withstand bursting forces due to the pressure of the

blood within the vessel and the expansile elasticity of the arterial wall, and this stress is transmitted to the knot.

*Tensile Strength Of Knots—"A" Silk Thread, Dry*

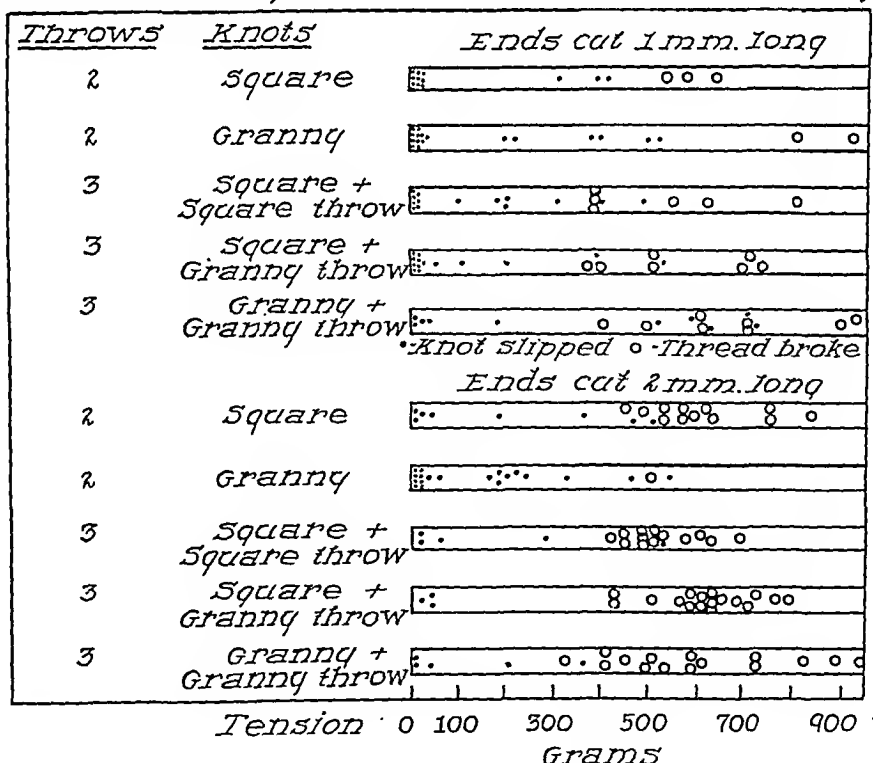


FIG. 3.—Strength and security of knots. Tests made with a tensiometer. Solid dots represent knots which came untied; circles knots which held until the thread broke. The amount of tension required to loosen or break the knot is indicated by the position of the dot or circle.

*Tensile Strength of Knots - No. 60 cotton Thread,  
Dry*

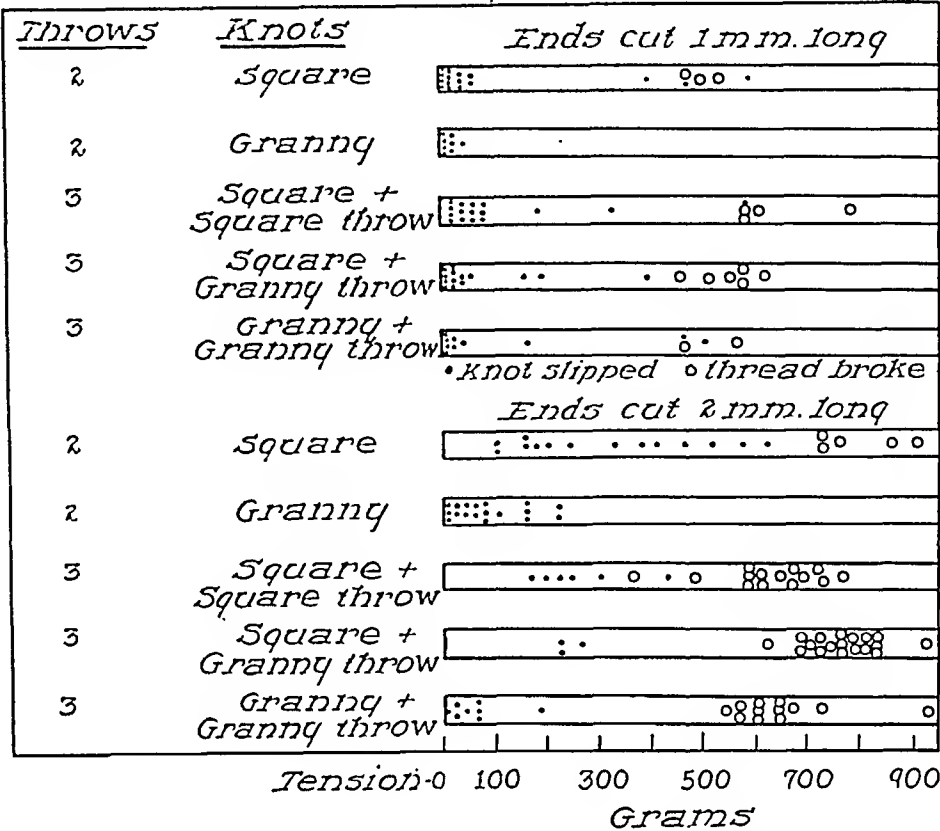


FIG. 4.—Strength and security of knots. Size "A" silk thread, commercial grade.

*Tensile Strength of Knots - No. 000 Catgut*

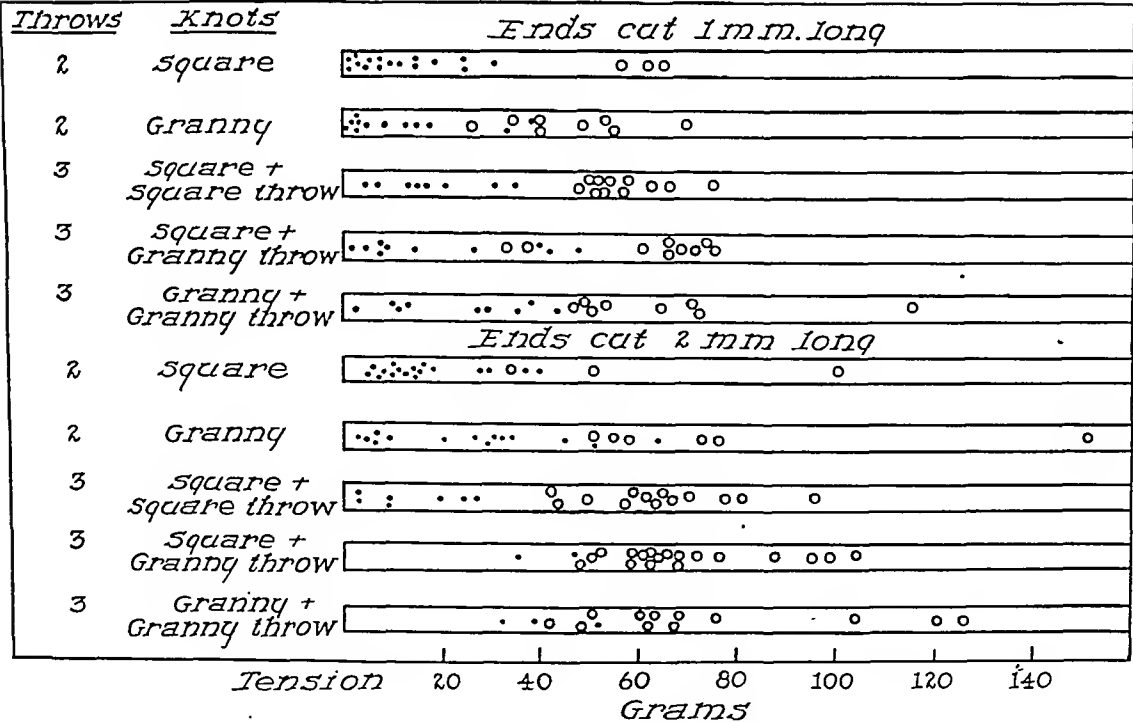






FIG. 5.—Strength and security of knots. No. 000 catgut. Catgut in general is less uniform than other suture material in tensile strength of the strand and in knot-holding ability. Similar results were obtained with plain and chromic catgut.

Figure 7B illustrates schematically the bursting forces felt by an abdominal incision. The suture represented there has to withstand the cumulative effects of (1) intra-abdominal pressure, (2) the lateral pull of abdominal muscles, and (3) edema or inflammatory pressure within the loop itself. A similar combination of tensions acts also upon lines of suture in the stomach or intestine.

*Tensile Strength of Loops  
#60 Cotton Thread*

				
Grams	811	1612	2864	3177
Ratio	1 0	2 0	3 5	3 9

(Factor of Knots eliminated)

FIG. 6.—Strength of loops.

animal tissues also and has wide applications in surgery. Mass ligatures are more apt to break or come untied than ligatures around small bleeding points or isolated vessels (Fig. 8). Large sutures are subject to greater tensions than small sutures. Four-zero silk is more than strong enough to tie a small artery like the thyroid, but might not hold the external iliac artery. The

The bursting strength of a loop is inversely proportional to the area which it encloses; or, to put it more accurately, the tension is proportional to the area which it encloses; or, to put it more accurately, the tension is proportional to the area enclosed. The results shown in Table II were obtained in tests made upon pneumatic tubes and balloons of various sizes, but this law of mechanics, well known to hydraulic engineers, applies to ani-

*Stresses Borne by  
Ligatures and  
Sutured Incisions*

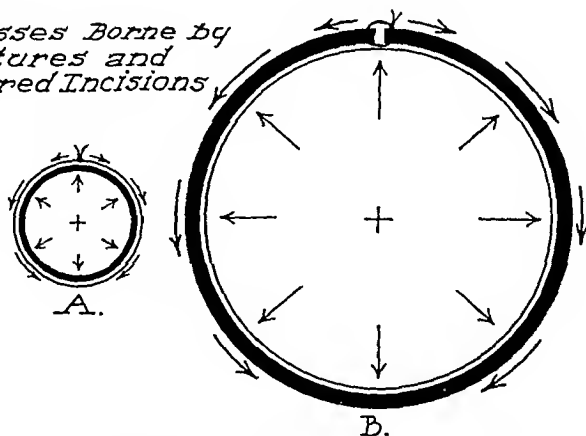


FIG 7.—Tensions felt by (A) ligatures and (B) sutured incisions.

larger the diameter of an organ or cavity, the greater the tension upon sutured incision (Fig. 9).

It follows that the size of suture and ligature material should be selected with a view to the tensions to which it may be subjected. The finest available cotton or silk thread should suffice to ligate ordinary bleeding points

The operator who places small, closely spaced sutures can afford to use fine suture material, whereas the operator who habitually takes large bites widely spaced must needs use coarser thread. A perforated peptic ulcer is more safely closed with two or three mattress sutures than with a relatively large purse-string suture.

This brings us to a consideration of rows of sutures. Tensions experienced by individual sutures are not easily measured in patients, but they

TABLE II—*Strength of Loops of No. 60 Cotton Thread*  
*Around Pncumatic Tubes or Balloons*  
*(Knots with many throes to prevent slipping)*

Diameter of tube or balloon	Pressure required to break thread	$\pi$ (the Greek letter "pi," i.e., 3.1416) x pressure
2.77 cm.	250 mm. Hg.	1505
3.44	204	1897
4.71	82	1426
8.81	22	1344
17.4	6.5	1355
24.0	3.5	1580

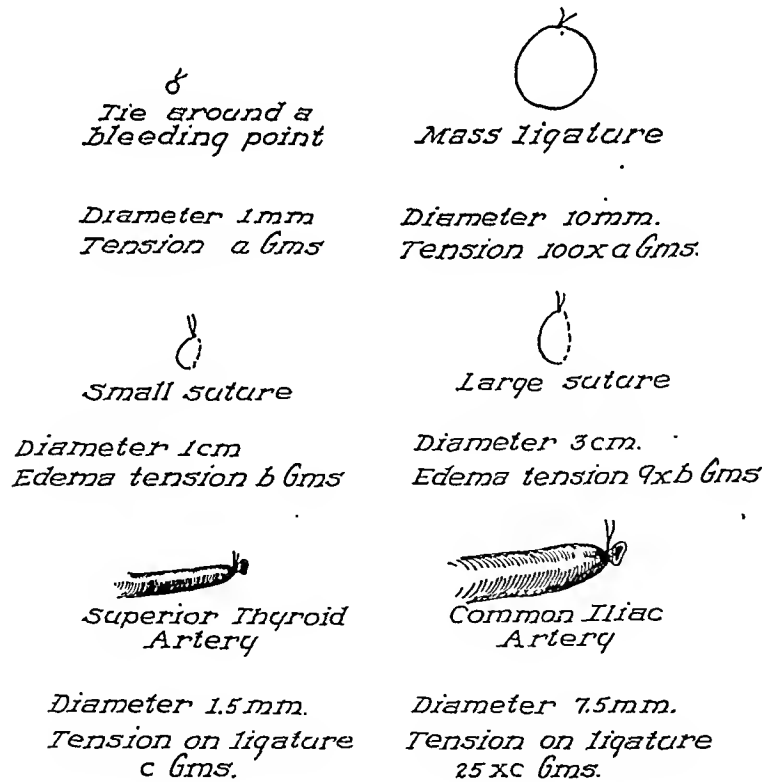


FIG. 8.—Other factors being equal, tensions on ligatures and sutures vary with the cross-section area enclosed by them.

can be studied in models and in freshly killed experimental animals, in which all the mechanical forces concerned are reproduced; and there can be little doubt that the effects observed in such experiments are similar to those which obtain in the living body. When sutures are uniformly spaced, the total tension felt by the suture line is found to be distributed equally

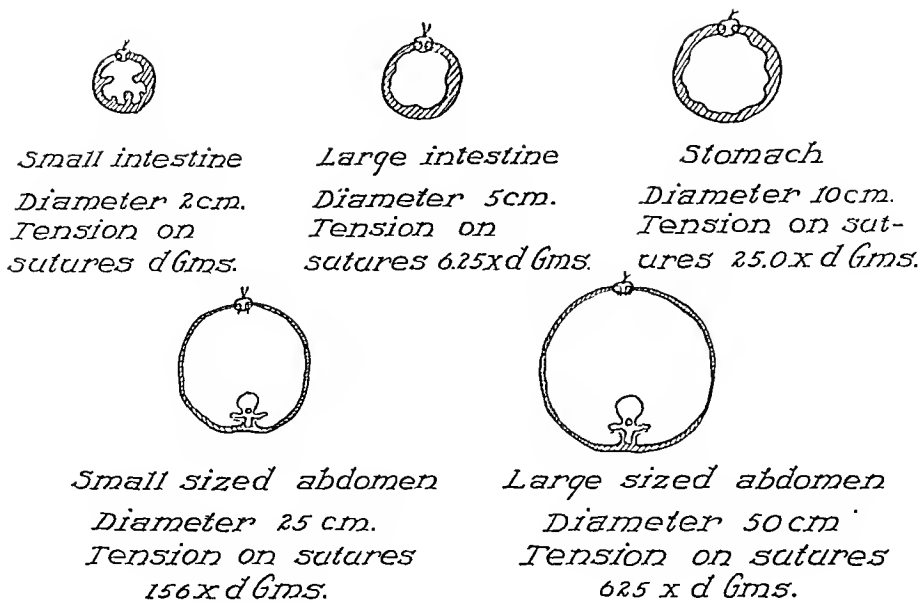


FIG. 9.—Effect of size of an organ or cavity upon the tension of sutured incisions. The values indicated in this diagram are used simply to illustrate the principle under discussion; actually, the total tension of sutured incisions is a complex matter with many variable factors involved.

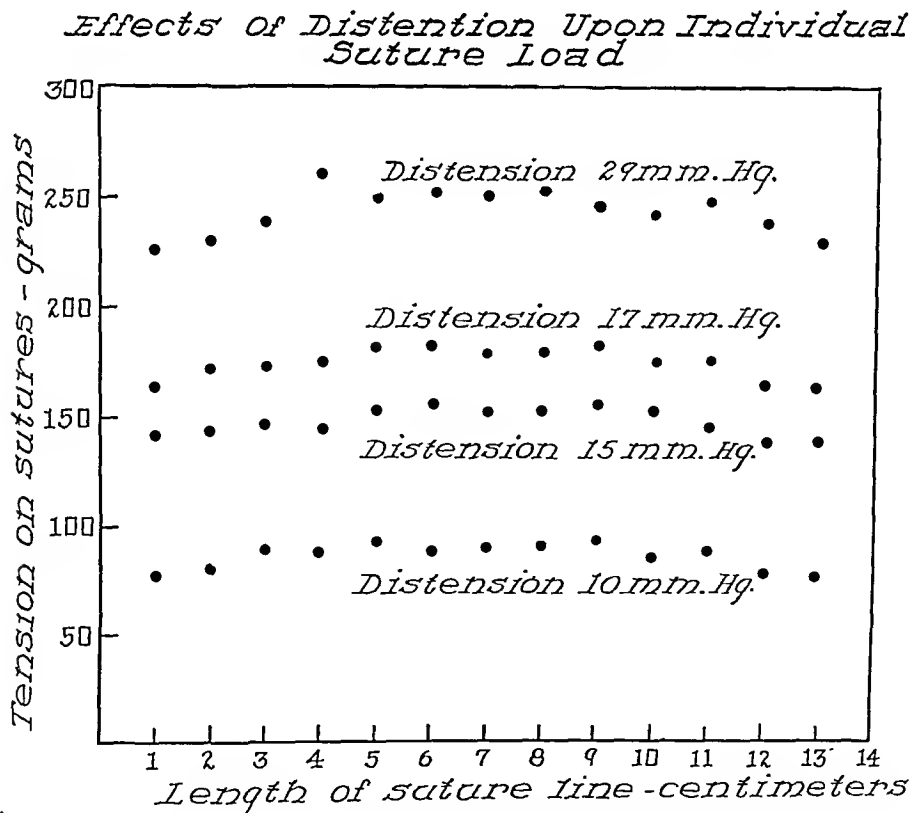


FIG. 10.—Distribution of tension between sutures in an incision, and effects of distention upon the suture load.

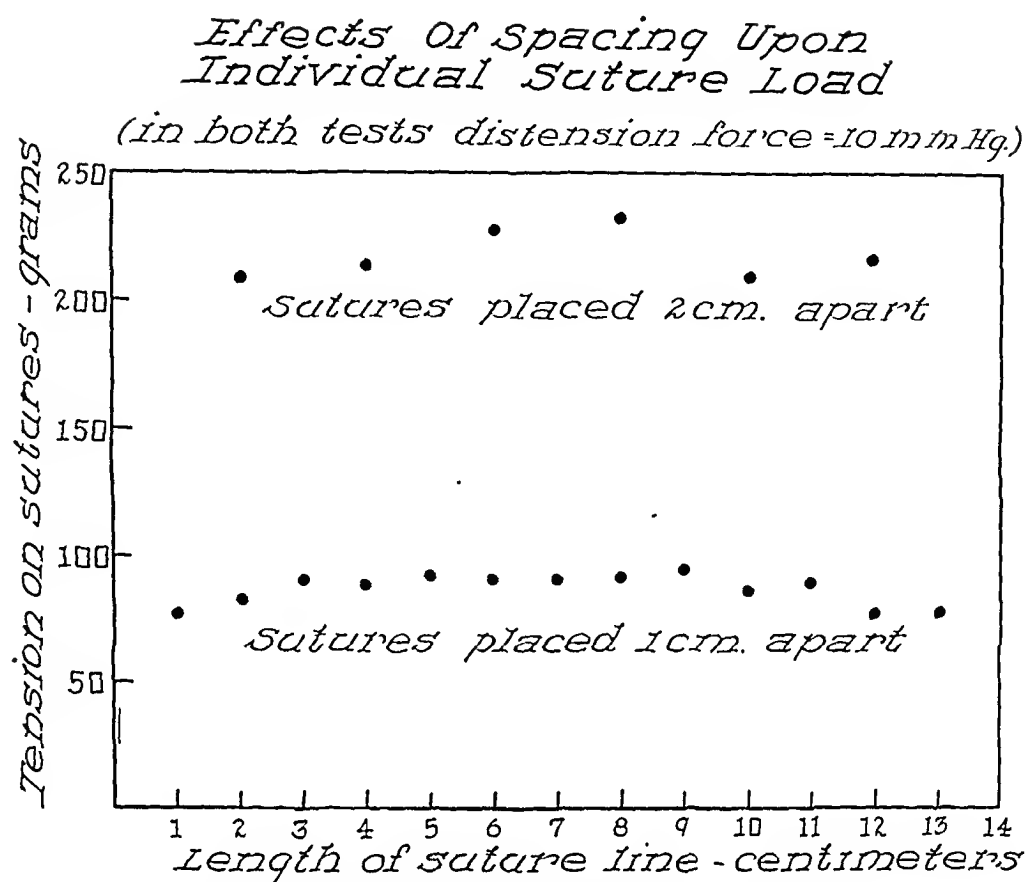


FIG. 11.—Effect of spacing of sutures upon suture load.

*Distension Pressures Required  
To Rupture Various Suture Incisions*

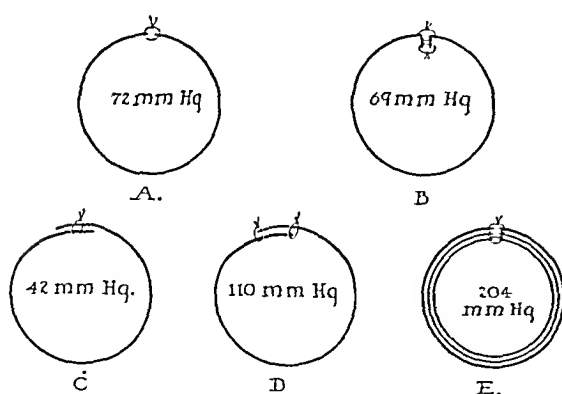


FIG. 12.—Results of tests made under comparable conditions to show the relative strengths of various sorts of closure. A, a single row of approximating sutures; B, a second, "reinforcing" row of invaginating sutures; C, imbrication with a single row of sutures; D, imbrication with two rows of sutures; E, 3 layers closed independently.

between the sutures (Fig. 10). In the case of an abdominal incision, the greater the intra-abdominal pressure, the greater the tension upon the entire suture line, and the greater the tension upon each individual suture. If there are fewer sutures more widely spaced, each suture then has to carry a larger share of the total load (Fig. 11).

Other factors being equal, the over-all tension on an incision is proportional to its length. There are usually more sutures in a long incision to share the load, however, so that the tension upon individual sutures is apt to be much the same, whether the incision is long or short. Should one suture

of a row slip or break, the tension which it has borne is immediately transferred to its neighbors. If, with the sudden increase in tension, those sutures break also, even greater strain is then thrown upon the next in line. Thus a sort of "chain reaction" may be set up with disruption of the entire row of sutures.

Figure 12 shows diagrammatically the relative strengths of various closures by layers. In the so-called reinforcing row (Fig. 12B), all of the tension is concentrated on the outer row; should that give way, the full force is then thrown on the inner row. The main advantage of that sort of closure is watertightness. Imbrication does not add to strength unless both edges are sewed down. A closure with three independent layers is three times as strong as a single layer closure.

#### BURSTING STRENGTH OF INTESTINAL CLOSURES OF DOGS

*(single row of interrupted sutures, tested one hour after closure)*

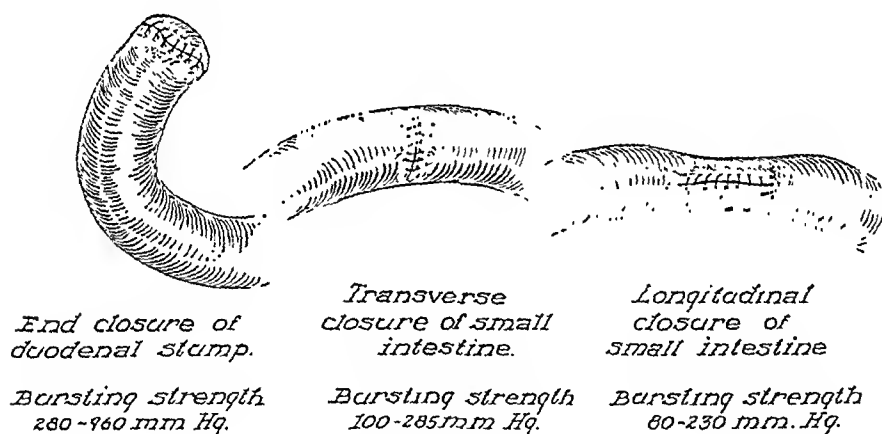


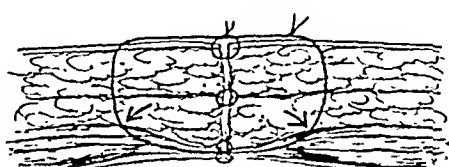
FIG. 13.—Bursting strength of intestinal incisions in dogs. Not infrequently in these tests the wall of the intestine ruptured before the suture line gave way or leaked.

Experiments in dogs show that a duodenal stump closed with a single row of well-placed, interrupted, inverting sutures of No. 60 cotton or 4-0 silk thread (Fig. 13) is able, without leakage or disruption, to withstand intraduodenal pressures of 280 to 960 mm. Hg.—pressures far in excess of anything ever encountered clinically. I am convinced that leakage of the duodenal stump is due not so much to weakness of sutures as to ischemia, necrosis, and cutting through of sutures, either because they were tied too tight, or because too much bowel wall was turned in and strangulated with multiple rows of sutures.

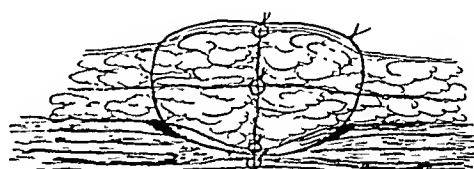
Since the transverse or cross section stretch of the bowel exceeds the longitudinal stretch (Fig. 13), intestinal distention puts less strain on transverse than on longitudinal incisions. For that reason end-to-end anastomoses are mechanically stronger than side-to-side anastomoses.

Another aspect of the problem is strength of tissues. Unless the tissue sewed is as strong as the suture used, variations in suture strength become irrelevant. Three variable factors must be considered in this connection. First, the sort of tissue one has to deal with. Skin and fibrous tissue are the toughest of the soft tissues; indeed, the suture-holding strength of most soft tissues depends upon the amount of fibrous tissue they contain. Thus the brain and spinal cord, containing minimal amounts of fibrous tissue, will scarcely support sutures, but the sutured sheath of a peripheral nerve will hold even under considerable tension. The seromuscular coat of the

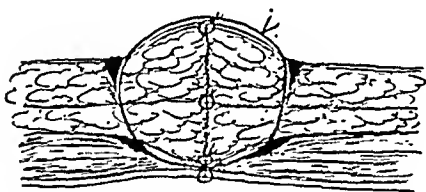
*Conventional Tension Suture*



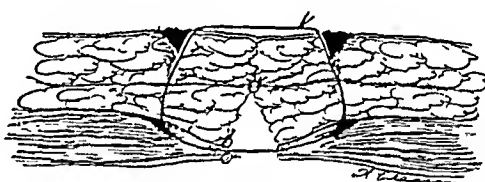
*A. When placed. Arrows show points of tension and poor support.*



*B. Third day. Beginning edema*



*C. Seventh day. Marked edema; tension suture approaches circular shape and cuts through skin and fascia.*



*D. Tenth day. Edema subsiding. Distortion of suture permitting disruption of wound.*

FIG. 14.—Drawings made from autopsy material showing the mechanical inefficiency of "stay" sutures commonly used to reinforce abdominal incisions.

intestinal wall is rather easily torn by sutures unless the thread has taken a bite of the tough fibrous submucosa. The second variable factor is the health of the tissues. With acute inflammation tissues become friable; with ischemia—we all tie our sutures too tightly—and with necrosis, tissues slowly give way before the advancing pressure of the thread and we say that the suture "cuts through." The third variable factor is the size of the suture material. The finer the thread, the more readily it will cut through either healthy or diseased tissue. Recently steel wire sutures have become popular; yet steel wire cuts through most soft tissues long before full advantage can be taken of its enormous tensile strength.

Technically, *strain* means distortion due to stress. An example of strain is provided by the conventional tension suture often used in closing abdominal



incisions. Figure 14 shows why that suture is inefficient mechanically and often fails in its purpose because of distortion. The lateral pull of the musculofascial layer is opposed only indirectly by the suture, much as a bowstring opposes the pull of an archer's fingers. Inevitable edema plays its nefarious role.

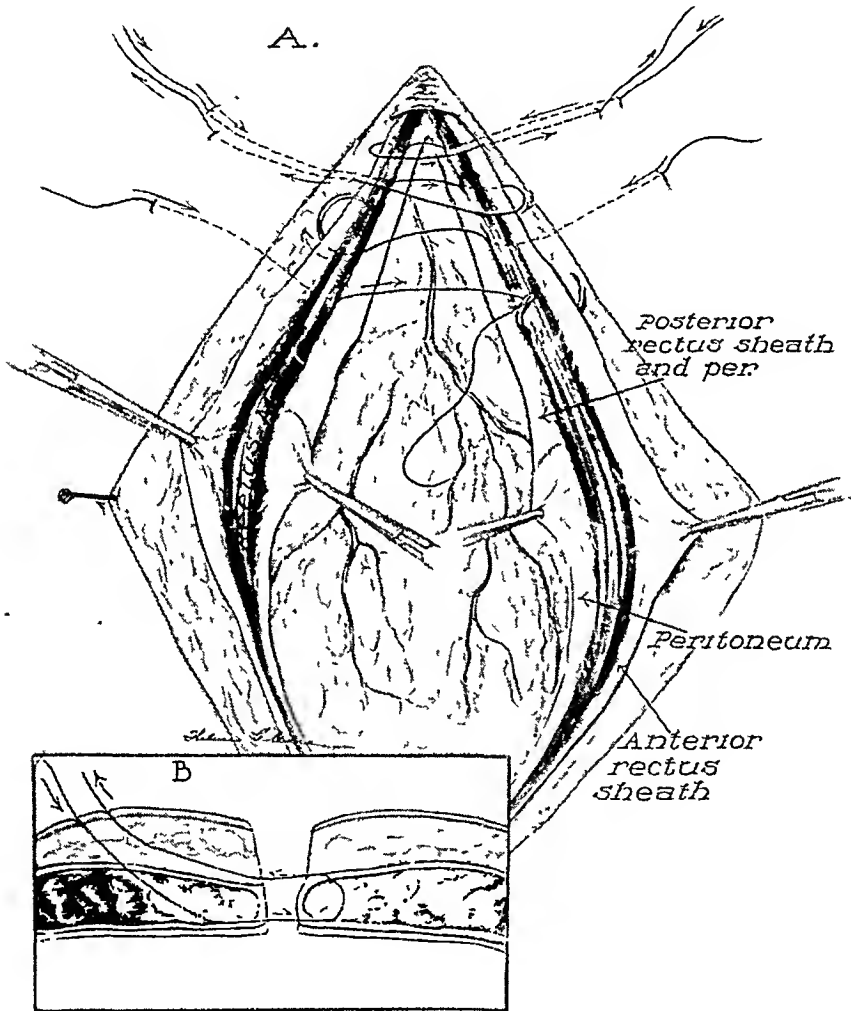


FIG. 15.—A new tension suture which enters the abdominal wall at a distance from the incision, crosses the incision to take a generous bite in the musculofascial layers of the opposite wall, and returns to emerge near the point of entry. The posterior rectus fascia should be grasped by this suture.

Figures 15, 16 and 17 illustrate a tension suture which has been used by the writer during the last two years with satisfaction. There are no closed loops to produce ischemia or to be affected by edema. These sutures, which are staggered, take generous bites of fascia and muscle so as to

minimize the danger of tearing or cutting through. They should be drawn just tight enough to approximate the muscles and fascia. Inasmuch as their pull directly opposes the strong lateral pull of those structures, they cannot be distorted to any extent, unless they break, however great the tension. These sutures can be adapted to paramedian, transverse, subcostal, hockey-

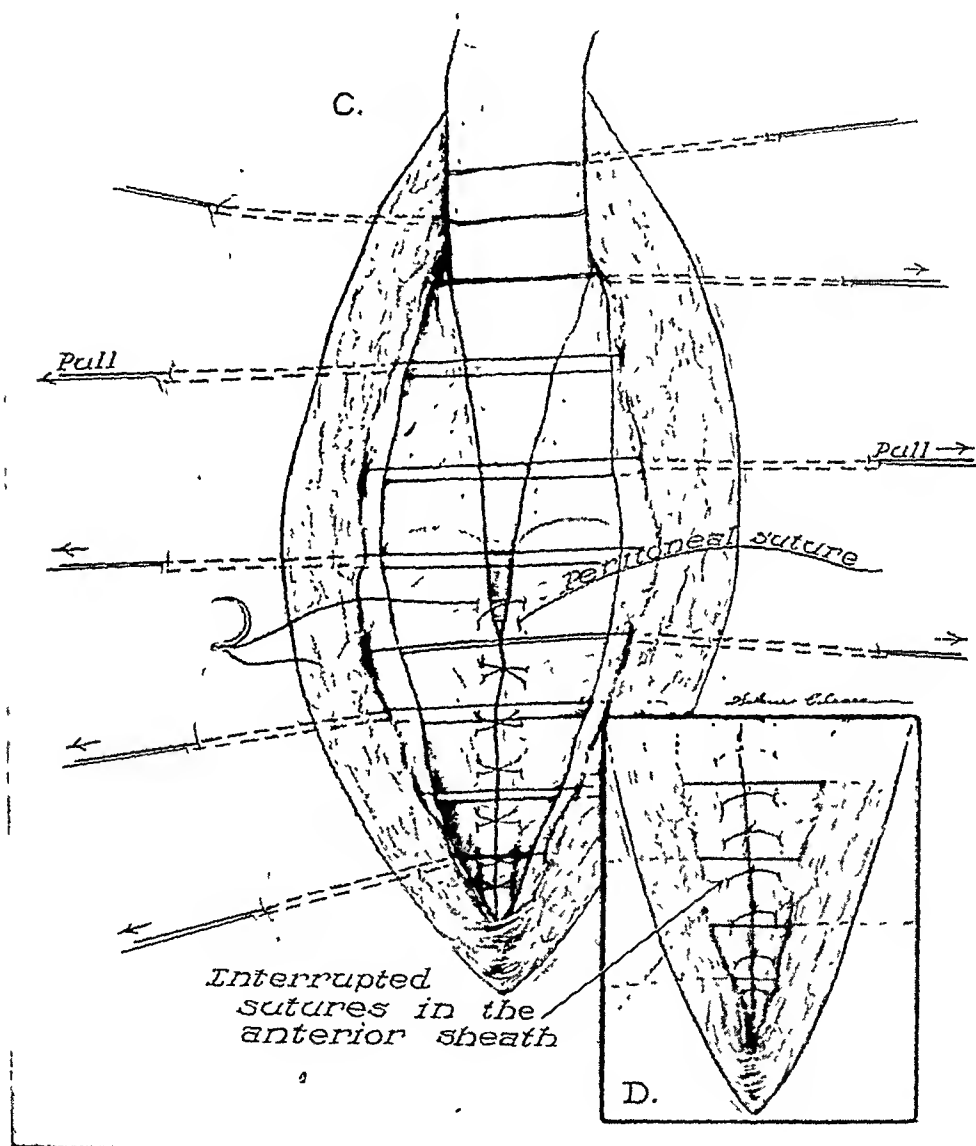


FIG. 16.—Further steps in placing the tension sutures and in closing the abdominal wall.

stick, and T-incisions. If desired, the ends may be tied over rubber tubes or rolls of gauze instead of the metal frame shown in Figure 17. The suture is readily removed after cutting one of the strands close to the skin.

If No. 2 or No. 3 silk or nylon is used, the combined holding strength of these tension sutures is very great, amounting altogether to some 200 or 300 pounds. Patients find them relatively comfortable since they do not tend to cut through or irritate the skin, since their firm support relieves

much of the pain of turning, coughing, and early ambulation, and since they obviate the necessity for tight adhesive strapping and supportive binders.

### SUMMARY

No reputable engineer attempts to construct a bridge without knowing first the stresses and strains to which his structure probably will be subjected,

the tensile and shearing strengths of his building materials, the calculated total strength of his design, and the margins of safety to be allowed. But in surgery, where the health or life of a patient may literally "hang by a thread," the caliber and sort of suture and ligature material to be used is too often left to guess or habit; the size and spacing of sutures, the number of rows to be used, the sort of knots to be employed, are often simply matters of hand-me-down custom, with scant reference to well-established laws of mechanical forces. Indeed, most surgeons have vague ideas about the amounts of stress and strain which lines of suture are apt to feel, or how best to meet those potential disrupting forces. To play safe, suture material is often used that is unnecessarily coarse, or wire that is many times stronger than the tissues being approximated, or tension sutures that are mechanically inefficient.

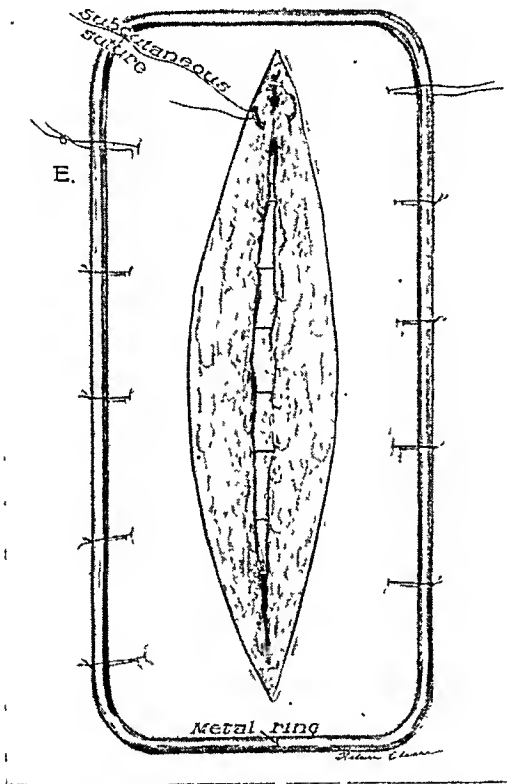


FIG. 17.—These tension sutures are staggered so as to avoid undue squeezing and ischemia of tissues. They are carefully adjusted and tied before the more superficial layers of the wound are closed.

The present paper attempts to explore that neglected but important aspect of operative surgery. Largely on the basis of some original investigations, it presents certain basic principles which should be followed, and offers some practical suggestions which (it is hoped) will give the surgeon better-founded confidence in his ligatures, anastomoses, and wound closures. A new tension suture is described, which is believed to be mechanically superior to the conventional through-and-through tension suture.

DISCUSSION.—DR. ALLEN O. WHIPPLE, New York: This subject is one that should be called to the special attention of our residents in training. I believe it is one that is too often neglected in the training of residents. To me this subject has always been of great interest and I have followed some of the earlier writings, particularly the subject of wound repair by Halstead, with extreme interest, and have found that his philosophy has held true throughout. He made certain statements without going into the details, trusting, I believe, to his teaching of his residents and to their own observations—and to me these have always been sound. One was that there was no point in using suture material that was more than twice as strong as the tissues in which the sutures were placed. Second, that non-absorbable suture material and catgut should not be used in the same tissues. The point that Dr. Price has brought out about the importance of eliminating tension on the suture line is something that should be emphasized over and over again. It is studies such as Dr. Price has presented that give real thought and real value to the training of residents, and I noticed in discussing this subject with a group of them recently that they took more interest in that than in almost any other subject. Unfortunately, Dr. Price had to present this material in rather rapid fashion, but I am sure that when we read his paper we will find sound philosophy in it.

# FURTHER STUDIES ON THE CYTOLOGIC METHOD IN THE PROBLEM OF GASTRIC CANCER \* †

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AND

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TWO YEARS AGO IN THIS LABORATORY cytologic study was made of the fasting gastric contents of 50 patients suspected of having cancer of the stomach<sup>1</sup>. It was learned that preparations with satisfactory cellular detail were usually possible, and that both benign and malignant cells from the gastric mucosa could be recognized. At operation 24 patients in this series proved to have carcinoma of the stomach; and a correct preoperative cytologic report had been made in 15. One additional cytologic report of cancer was rendered in a patient who showed a benign gastric ulcer after pathologic study. We were particularly impressed by finding malignant cells in two very small cancers, one of them non-invasive (carcinoma-in-situ).

In planning a more detailed study of this technic, particular emphasis has been placed on the method of collecting fluid which is most likely to secure and preserve a cellular specimen representative of all areas of the stomach. Several facts make this more difficult than is the case with most other fluids. One is the rapid action of the digestive ferments present; another is the constant tendency of the intestinal current to sweep material out of reach of the tube, particularly in the case of lesions in the distal segment of the stomach.

## METHODS

Both Rehfuss and Levine tubes have been used, in some instances with fluoroscopic check on their position. In a number of patients the undiluted fasting content of the stomach has been examined; others have been allowed to drink water as the tube was passed. After evacuation of the stomach we have irrigated it with saline, with 7% alcohol, or with a 5% suspension of clove oil. The secretion stimulated by parenteral injection of histamine has been examined in the majority of cases. Repeated study with varying techniques has been possible in a few instances.

Out of these observations a standard procedure has been evolved. A number of additional openings are made in a size 14 Levine tube. It is introduced through the nostril in the usual manner for a distance of 75 centimetres; the patient is allowed to drink tap water to facilitate this maneuver. The stomach is then evacuated as completely as possible. This is our first specimen. One hundred cubic centimetres of normal saline is injected, the

\* This study was supported by a grant from the American Cancer Society.

† Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

tube is clamped, and the patient lies first on one side, then on the other, then on his face, and finally sits up or walks. The saline is partially withdrawn and reinjected several times during this procedure. Finally the stomach is again aspirated until empty. Both samples of fluid are centrifuged immediately for 20 minutes at about 2000 r.p.m., the supernatant fluid poured off, and thin smears made from the sediment. These are fixed and stained by Papanicolaou's method<sup>2</sup>.

#### RESULTS

To date, 48 patients have been studied in this fashion. The specimens were unsatisfactory in three, all of whom had obstruction and an appreciable degree of gastric retention. At operation two had benign ulcers and one had carcinoma.

Eminently satisfactory cellular preparations were secured in the remaining 45 cases. Operation has disclosed carcinoma of the stomach in 14, 12 were diagnosed correctly by our method. One other report of malignancy has been rendered in a patient with no detectable gastric lesion and in whom no operation has been performed. One patient proved to have malignant lymphoma of the stomach. The cytologic preparation in this instance contained no abnormal cells of any type.

#### SUMMARY

Various methods of preparing cytologic specimens from gastric fluid have been studied and a standard procedure evolved. Satisfactory cellular detail has been noted in all cases except those where appreciable obstruction exists. The accuracy of this method of diagnosis in our hands has increased since the introduction of the modifications described herein.

#### BIBLIOGRAPHY

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- <sup>2</sup> Papanicolaou, G. N.: *New Procedure for Staining Vaginal Smears, Science*, 95: 438-439, 1942.

DISCUSSION.—DR. JOE V. MEIGS, Boston (closing): We feel that the diagnostic method presented by Dr. Ulfelder is perhaps a partial answer to the many times I have listened to surgeons present the tragic results of surgery for carcinoma of the stomach. I have heard presentations of a hundred patients operated upon and at the end of five years only a few were alive. If by this method we can find even only one early carcinoma—and we have found more—its value is proven. We believe it is better sometimes than x-ray examination, better sometimes than gastroscopic examination. We may be able to pick up cases that have a chance for cure. It is a very fussy business and it needs an expert. Recently Mrs. Graham in our Vincent Hospital Laboratory has told me that within the last eighteen months any patient that she said had a positive smear for carcinoma of the cervix had carcinoma of the cervix. She has picked up between 25 and 30 unsuspected cancers of the cervix. It is wrong for us to think that as clinicians we can do this work. It should be done by experts. At a recent meeting in Boston, under the auspices of the American Cancer Society, it was generally recognized by the pathologists that it was their duty to teach this method

of diagnosis to their residents, so as to spread the proper means of technic throughout the country. The best cytologists can make mistakes. It seems to me it is essential that we have under tutelage and instruction a goodly number of men who will be experts in making cytologic diagnoses. I believe earlier diagnosis can be made through this method than by any other we have at present.

# ANTERIOR RESECTION FOR MALIGNANT LESIONS OF THE UPPER PART OF THE RECTUM AND LOWER PART OF THE SIGMOID\*†

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THE OPERATION OF ANTERIOR resection for lesions of the terminal part of the large intestine with re-establishment of intestinal continuity has been criticized by many authors as not being sufficiently radical. The present paper is an evaluation of the operation. The efficacy of any surgical procedure for cancer is judged by the number of persons undergoing the procedure who are alive five years or more and not on an anatomic basis—the extent of the excision.

This study is limited to the most controversial segment of the large intestine; namely, the distal 20 cm. It is for this region that new procedures are constantly being advocated and interest in old ones is being rekindled. A matter of 3 or 4 cm. from the dentate line makes the difference between an operation involving a permanent colonic stoma and one in which intestinal continuity can be re-established. While the majority of patients become adjusted to a permanent colonic stoma, there are some who have difficulty in its management. It should be remembered that those "cured" by anterior resection can live normally in every respect.

Because it is so important in determining the possibility of re-establishing intestinal continuity, I have considered the cases in this study in respect to the distance of the lower edge of the lesion from the dentate (pectinate) line as measured by the proctoscope. By studying the prognosis for each segment separately one could determine the lowest level at which it is sage to apply the procedure. I have avoided the use of the term "rectosigmoid" since it is merely a clinical designation for the rectosigmoidal juncture. Variation of the length of the rectum and of the level of the pelvic peritoneal fold, change of the length of the rectum after mobilization, shrinkage of the tissue by the time the pathologist measures it and differences in the interpretation of descriptive terms have led me to depend on the distance measured proctoscopically.

## DEVELOPMENTAL BACKGROUND

The operation of anterior resection had been applied to lesions of the sigmoid before 1910, at which time primary anastomoses were performed, a large rectal tube being placed through the anastomosis for the purpose

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\*Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

†I am indebted to Dr. A. L. Lichtman and Dr. G. Lowe for some of the material used in preparation of this paper.



of decompression. The application of the procedure to lesions of the rectum came about in a roundabout way. A series of operations were performed in which continuity of the bowel was not re-established. In the first stage sigmoidal loop colostomy was performed; in the second procedure the lesion and its mesentery were excised and the sigmoidal and rectal stumps were closed. If the patient survived, subsequent exploration and re-establishment of intestinal continuity were warranted. It became customary to advise the patients that if they got along well they could return in six to 12 months for sigmoidorectostomy. The satisfactory survival rates, despite extensive lesions of high grade, suggested that the intestinal anastomosis could be performed at the second stage of the operation. Three facts were apparent: First, the rectal stump can survive if supplied by the inferior hemorrhoidal vessels alone, regardless of the fact that the textbooks have denied this; secondly, Sudeck's point is not as critical as described and, thirdly, it is possible to excise sufficient tissue in the mesocolon and distal portion of the sigmoid and to obtain good clinical results. Apparently it sufficed to remove only 3 or 4 cm. of bowel distal to the lesion. This latter observation was difficult to reconcile with Miles's<sup>9</sup> work but subsequent careful study of cleared specimens showed that the occasional distal spread of carcinoma to lymph nodes beyond 2 cm. is due to proximal blockage.<sup>1,7,13</sup> In such instances it is possible that no surgical procedure is sufficiently radical to include the centrifugal spread from such obstructed lymphatic drainage.

The procedure outlined here I first performed in 1930. It has been reported previously in detail.<sup>2-4</sup> Up to 1938 the majority of such operations were carried out in three stages including preliminary transverse colostomy. In the second stage the lesion was removed and colosigmoidostomy or colectostomy was performed through a low left rectus incision. In the third step the colonic stoma was closed after suitable clamping of the spur. Since 1938 colostomy has been performed at the time of resection unless there was severe obstruction. With progress in methods of decompression and with the preoperative use of sulfasuxidine or sulfathaladine and vitamin K, antecedent colostomy is being performed in fewer cases than before. At present, with few exceptions, patients come to the operating room well prepared by administration of sulfasuxidine and rectal irrigations, and the surgeon has definite proctoscopic information regarding the grade, level, mobility and extent of the lesion. This has reduced the mortality rate and permitted the performance of an open accurate anastomosis.

The performance of sigmoidal colostomy as a preliminary or emergency procedure in these cases makes the resection extremely difficult by limiting the mobility of the colon and frequently dissection of the colonic stoma from the abdominal wall is necessary in addition to the performance of transverse colostomy.

Since 1941 such patients have received preoperatively a minimal daily oral administration of 12 Gm. (180 grs.) of sulfasuxidine or sulfathaladine

for a period of three to eight days. In addition, 5 Gm. of sulfathiazole is scattered intraperitoneally at the close of the operation. I feel that this chemotherapy has produced a distinct reduction of the mortality rate. Culture of stools after adequate preparation with the insoluble, poorly absorbed sulfonamides has shown a dramatic fall of the count of coliform organisms. This advantage is appreciated most by the surgeon who prefers an open anastomosis. With the use of the sulfonamides, peritonitis has become much less common. In addition, there has been a fall in the incidence of thrombophlebitis and pulmonary emboli, probably resulting from a reduction of the contribution that is made by infection in these complications.

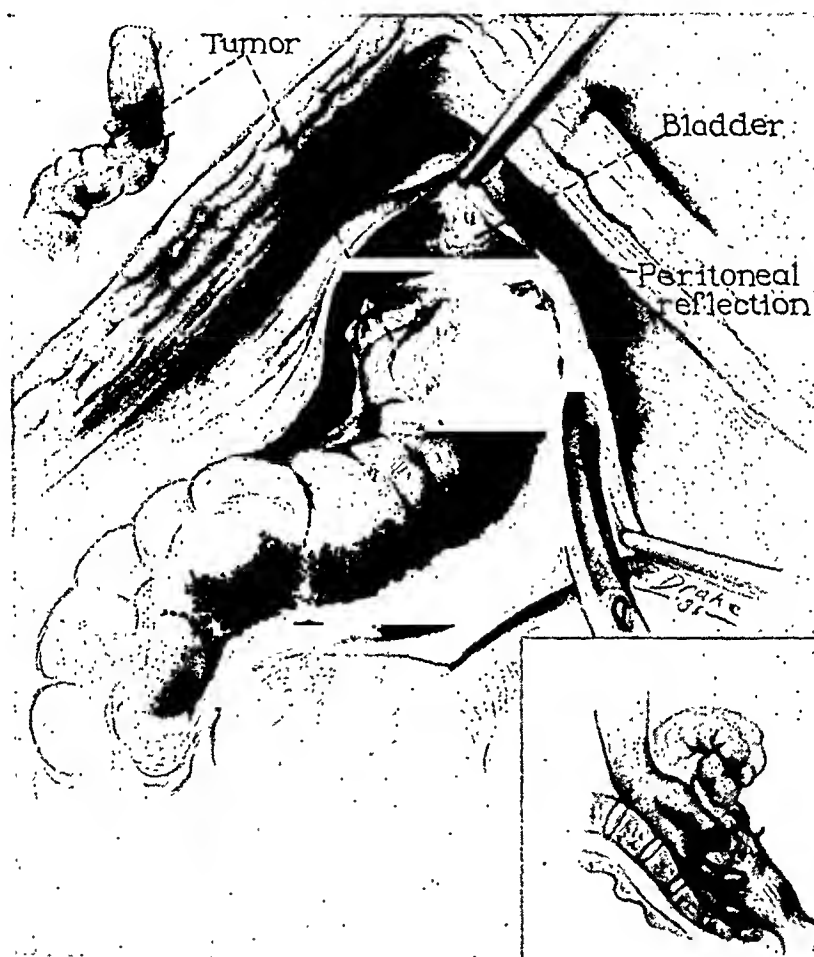


FIG. 1.—The peritoneum is incised as indicated, freeing the sigmoid and rectum. The rectum is mobilized from the sacrum as shown in the lower right insert.

The use of streptomycin was for a time thought to be as effective in reducing the coliform count as was that of either of the aforementioned sulfonamides. It has been demonstrated that streptomycin does lower the bacterial count in the bowel but for two to three days only. After this period, regardless of the amount of streptomycin administered, the coliform organisms return to their normal count. It would seem, therefore, that streptomycin must be considered as an adjunct only to sulfonamides in surgery of the colon.

## THE TECHNIC OF LOW ANTERIOR RESECTION

The operation is performed with the patient in a steep Trendelenburg position and a long left rectus muscle-splitting incision is used. The pelvic colon is mobilized by dissecting the fused lateral peritoneum free from the mesosigmoid. The peritoneal incision is outlined so that an adequate cuff of peritoneum is excised with the colon, passing up the lateral aspect, curving around the rectovesical or rectocervical space and passing back on the mesial aspect (Fig. 1). The entire left portion of the colon is then mobilized by incising the lateral peritoneal reflection of the left paracolic gutter as far as the splenic flexure. Both ureters are identified and isolated.

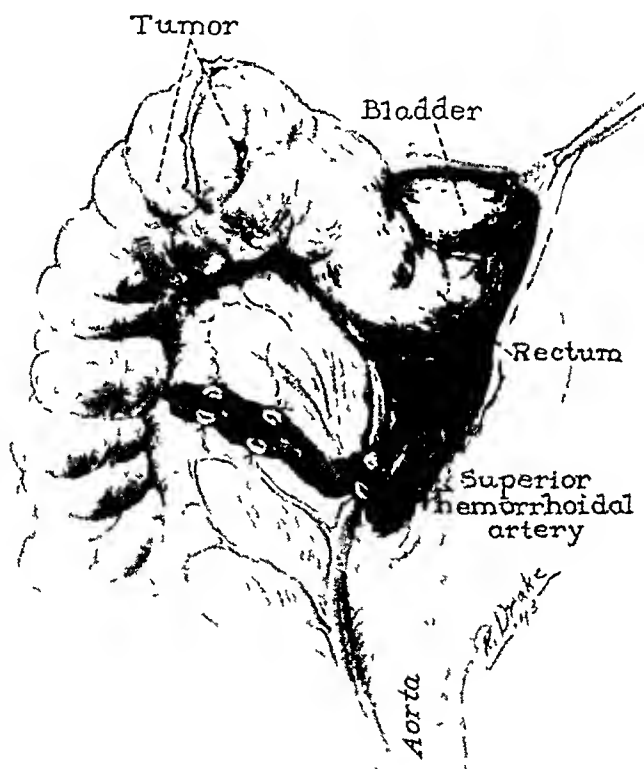


FIG. 2.—After mobilization of rectum and sigmoid the site for the ligation of the superior hemorrhoidal or inferior mesenteric vessels is selected and a V-shaped section of mesentery is excised.

The rectal ampulla is then mobilized from the hollow of the sacrum as far as the coccyx (Fig. 1) and from the vagina or seminal vesicles and prostate by blunt and sharp dissection. Usually in the case of a low lesion, such as is under consideration here, a large portion of the branches of the middle hemorrhoidal vessels, which are of irregular distribution, must be sacrificed.

The mobilized mesocolon is then transilluminated and the vascular pattern is determined. When the mesentery is very fat one must depend on palpation. The point of ligation of the inferior mesenteric or superior hem-

orrhoidal vessels is then outlined. My colleagues and I do not recognize any critical point in this determination, rather depending on the precepts of rational cancer surgery and providing the correct amount of excision to allow the sigmoid or descending colon, as the case may be, to reach or bridge to the rectal or rectosigmoidal transection without tension. It should be recognized that the mesentery of the sigmoid usually is omegoid and that one obtains more colon to reach into the pelvic outlet by going higher up with the mesenteric ligation (Fig. 2). Because of this the low resections themselves insure the adequate resection of the pelvic mesocolon since often it is impossible to obtain enough mobile colon unless one ligates rather high up on the inferior mesenteric artery. While in the earlier developmental years, resections were somewhat less radical, there has been a tendency in the past five years to standardize the operation more or less so that as much bowel as possible is removed even if the lesion is situated above the pelvic peritoneal fold.

If one does not feel certain of the pattern of the circulation to the upper segment, the bowel may be transected before the inferior mesenteric artery is ligated and the effect of ligation at the selected site may be determined by pinching the artery. Instead of depending on the color of the intestine it seems wiser to look for the pulsations in the arteries as they enter the colonic wall. After ligation of the vessels and transection of the colon the intestine is reflected over the pubis. Steady slow traction is exerted on the rectum with a hand deep in the hollow of the sacrum. The smooth muscle of the rectum and vascular stalks relaxes slowly. The curves, valves and folds of the rectum straighten and give more length. The anal canal and levator ani muscle are slowly funneled into the pelvic bowel. This maneuver may permit ligation of the rectal stalks as far lateral as 4 cm. to include any lateral spread in this area. These measures permit placement of rubber-covered intestinal clamps (Fig. 3) well below the lesion in selected cases even when it is 6 to 8 cm. from the dentate line. Actually, after mobilization of the rectum, the lesion is 10 to 12 cm. from the dentate line and one can resect the normal rectum at least 3 to 4 cm. below the lesion. In order to determine completeness of resection, frozen sections of the distal portion of the resected rectum are made routinely and thus a check is made on the surgeon's ability to palpate the lowest limit of spread.

The colon is then prepared for anastomosis to the rectum by placing another especially constructed rubber-shod curved intestinal clamp close to the end. The fat must not be cleared from the edge too extensively or the blood supply which enters the colon through the base of the fat tags will be sacrificed. The curved clamps on the colon and the curved clamps on the rectum are placed side-by-side (Fig. 3) in the deep pelvis and an open end-to-end anastomosis is performed without tension. Since the posterior portion of the rectum is thin and devoid of serosa only a single posterior row of stitches is placed. Anteriorly the rectum is thicker and a second

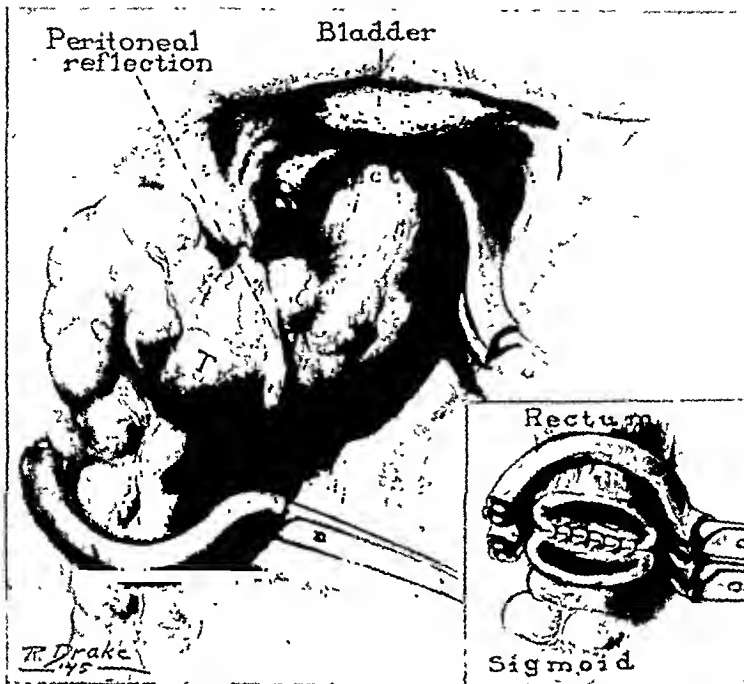


FIG. 3.—Curved intestinal clamps are placed beyond the lines of resection of the intestine. After the segment is resected the clamps are placed side by side and the open colorectostomy is performed as indicated in the insert.

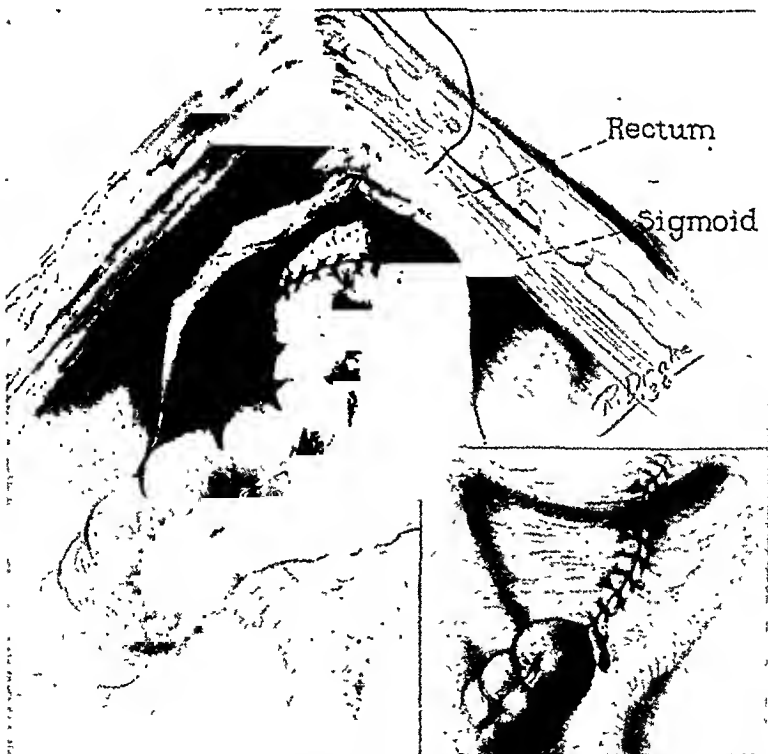


FIG. 4.—The pelvic peritoneum is closed at a higher level, which makes the anastomosis retroperitoneal. The drain has been omitted from the drawing.

inverting row is feasible. Any so-called aseptic anastomosis in this region is a gymnastic feat attended by difficult clamp maneuvers deep in the pelvis, danger of tearing the rectum, the hazard of catching the opposite mucosa to create a persistent diaphragm or of perforating the rectum in forcing the anastomosis open, and finally the possibility of a poor anastomosis. A valuable extra centimeter or more of rectum may be consumed in the process. Furthermore the posterior rectal wall is so thin that every stitch passes into the lumen and occasionally tears the rectal wall. For these reasons one questions how aseptic the closed anastomosis is.

In concluding the operation, 5 Gm. of sulfathiazole is dusted into the region of the anastomosis, a Penrose cigaret drain is placed in the hollow of the sacrum, emerging through the lower angle of the incision, and the peritoneum is sutured around the colon to reconstruct the pelvic floor proximal to the anastomosis (Fig. 4). The incision is closed after a loop of the transverse colon has been brought through the omentum and out of the upper angle of the incision to serve as a temporary colonic stoma and the omentum is brought down to cover the loops of intestine.

In the early cases the drain was brought out through an incision just in front of the coccyx. While the drainage is excellent, this introduces difficulties in draping the patient so that the assistant can make the stab wound to draw the drain through. Furthermore, the site of drainage is uncomfortable to the patient and it is easily contaminated and favors temporary fistula at the site. My colleagues and I have found that a drain brought out suprapubically is satisfactory and usually we begin to remove it about the eighth postoperative day. In cases in which there has been considerable perforation or soiling, sulfadiazine is administered postoperatively. Otherwise it is not necessary unless some abdominal or pulmonary complication indicates its use. Sulfasuxidine is administered only when a fistula or leak presents. When proximal colostomy is performed, a paste of sulfasuxidine can be instilled into the distal loop. The colonic stoma is opened by cautery incision in the patient's room from 18 to 24 hours after operation.

The colonic stoma usually is closed three to four weeks after the anterior resection. In preparation for the closure, patency and healing of the anastomosis are tested by passing water downward from the distal loop of the colonic stoma and upward from the anus. If a proctoscopic examination is made in the interval before closure the anastomosis is occasionally found to be as small as 2 cm. in diameter. A proctoscopist who has not encountered similar cases before will be distressed over the finding and will occasionally advise against the closure of the colonic stoma because of stricture. However, it has been found that although the lumen at the site of anastomosis may appear small the function is satisfactory and proctoscopy no longer is performed on such patients before closure of the colonic stoma. The free passage of water up and down through the anastomosis

is accepted as adequate proof of satisfactory function. Normally, the recto-sigmoidal junction is the narrowest part of the colon and such narrowing is consistent with normal function. The subsequent passage of fecal matter is the best dilator and at a later time the anastomosis will be found to be much larger than before. Delay in closure will only serve to permit further narrowing because of disuse and scar formation (contraction).

Leakage from the site of anastomosis occurred in 12 cases but with the proximal temporary colonic stoma, there is little febrile reaction and there is merely a delay of an extra week or two for the fistula to close before proceeding with closure of the stoma.

The preoperative preparation employing sulfasuxidine and the technic of closure of the colonic stoma were reported in 1944.<sup>5</sup> That report presented data on 102 cases in which colonic stomas made in various surgical procedures were closed by a standardized intraperitoneal procedure without a single death. Since then, the closure of colonic stomas has been performed with two deaths. The mortality rate for the entire series of closures is 0.6 per cent. In the deaths mentioned, one was caused by coronary occlusion. The patient had suffered from angina for five years. The cause of the second death was probably peritonitis. Necropsy was not permitted. A fecal fistula developed in three cases. In three cases there was purulent drainage and escape of gas. Five of the fistulas closed spontaneously within two months. In the remaining case the escape of gas occurred intermittently for ten months and then the fistula closed spontaneously. This would appear to demonstrate that the added risk of temporary colostomy is small if full advantage is taken of chemotherapy before and during closure of the stoma.

During the past five years, postoperative roentgen therapy has been used as an adjunct to surgical treatment in a series of patients whose lesions had progressed to the state of nodal involvement. An impression that this may be of value has been obtained from sporadic cases in which it was tried. The consensus at present seems to be that roentgen treatment is of little or of no value. Definite information on this matter will not be available for some time.

*The question of provision of a temporary colonic stoma.*—Previous to the advent of the sulfonamides, numerous methods of decompressing the colon proximal to the colorectal anastomosis were investigated but the provision of a temporary defunctioning loop type of transverse colonic stoma proved apparently to be the safest procedure. Enterostomy, appendicostomy and cecostomy were less efficient. A rectal tube with its orifice proximal to the anastomosis occasionally was responsible for ulceration and perforation of the colon and frequently became plugged. Preliminary sigmoidal colostomy has many disadvantages, which have been outlined earlier in this paper. The advent of sulfasuxidine warranted re-evaluation of the safety of omitting colostomy. The problem was approached with an open

mind but, at present, the mortality rate is considerably higher when colostomy is omitted than when it is included. The possibility exists that the introduction of coliform-effective antibiotics may make anastomosis without proximal colostomy safe if the lesion is above the pelvic peritoneal fold. Analysis of recent series of cases of anterior resection without colostomy<sup>8,11,12</sup> reveals that many of the lesions were above the pelvic peritoneal fold; yet in 10 to 20 per cent of the cases colostomy had to be performed as a post-operative emergency operation.

The omission of temporary colostomy in cases in which the lesion is near or below the pelvic peritoneal fold is fundamentally dangerous because the blood supply to the distal segment has been decreased. The sigmoidal anastomotic vessels above and the inferior hemorrhoidal vessels below provide a marginal blood supply that is adequate for healing under ideal conditions but not under strain. It has been long realized that anastomosis of a serosa-covered segment of bowel to a segment devoid of serosa requires 14 to 21 days to heal completely. Pemberton<sup>10</sup> has recently demonstrated by means of roentgenographic study of the segment of bowel distal to the colonic stoma in cases of low anterior resection of the lower part of the sigmoid and of the upper part of the rectum that at the site of the anastomosis barium often leaks into the pelvis or the hollow of the sacrum. Such leakage must then occur in many cases in which a colonic stoma is not established. Proximal colostomy seems indicated also if the lesion is adherent to the posterior vaginal wall, for the branches of the middle hemorrhoidal artery which supply the vaginal wall are often sacrificed in the dissection. Rectovaginal fistula may develop in such cases, especially if a temporary colostomy is performed. Closure of the stoma is then deferred for a month or two; this is occasionally necessary for complete healing in cases in which a portion of the vaginal wall has been excised.

I have applied the technic outlined in this paper in 523 cases, the first operations having been performed in 1930. In 46 cases, even though the distal loop was long enough to permit exteriorization, a short mesentery, obesity, intussusception of the growth, or some anatomic variation made anterior resection the procedure of choice. In 477 cases the lesion was 20 cm. or less from the dentate line. Of these operations, 39 were palliative and the procedure was performed in the face of distinct nodular metastasis to the liver. A number of these patients lived for more than a year. The lesion had invaded the wall of the bladder extensively in 12 of the cases and simultaneous partial cystectomy was performed. The latter group of cases was included in a recent report.<sup>6</sup>

*Age.*—The average age of the patients was 53.8 years. The youngest patient was 7 years of age and it is gratifying to report that this boy is still alive seven years after operation. Two of the patients were 79 years old.

*Sex.*—Of the 426 patients 55.6 per cent were male and 44.4 per cent were female. However, if the cases are analyzed it can be seen that the



worst lesions are found among females. Thus, in 24 of 37 cases in which there were high-grade malignant processes with nodal involvement the patients were female. In 28 of 40 cases in which the patients were less than 36 years of age, the patients were female. If one examines the lesions between 6 and 10 cm. one will find that the male to female ratio is 40:60. As the level proceeds toward the dentate line the proportion of females increases and the grade of the process rises, as has also been noted when one approaches the dentate line from below. To summarize: The lesions among females tend to be of higher grade and closer to the dentate line than among males, while the patient tends to be younger.

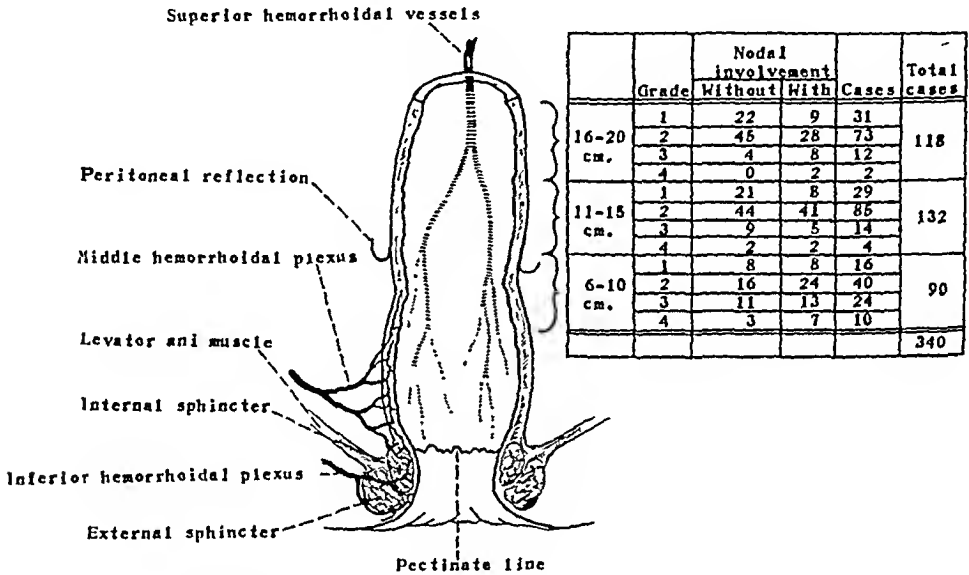


FIG. 5.—Distribution of the malignant lesions in the 340 cases in which the operation of anterior resection was applied. Palliative operations are omitted. The number at each stated distance from the pectinate (dentate) line is given in the figure. The incidence of each grade with and without nodal involvement is also included.

*Pathologic character and location of lesions.*—The lesions in the 426 cases were all adenocarcinomas. Figure 5 shows the distribution by grade and nodal involvement for each 5 cm. segment in the region under consideration. The specimens were not cleared but were examined by multiple incisions in the search for lymph nodes. All of the lesions were segregated according to Dukes's classification and graded by Broders' method. Few lesions of type A were found in the series. The majority of the lesions removed by anterior resection were perforating, since the rectum is so thin that all layers are usually involved before detection. Twenty lesions (5.9 per cent) were of the mucous (colloid) type. Five were described as papillary. Multiple synchronous malignant lesions were found in 18 cases (5.3 per cent). Gross venous or perineural involvement, which invariably gives a poor prognosis, was noted in seven cases.

The lesions were separated into groups depending on their distance

from the pectinate line (Fig. 5). This was done in order to learn if there was a difference between the survival rates of patients having lesions at various levels in the bowel, for if the operation of anterior resection is not sufficiently radical the survival rate of those having the lowest lesions would certainly be less than that of those found to have lesions above the pelvic peritoneal fold.

*Resectability, indications and limitations of the method.*—The examination of any large series of cases in which there are lesions in this zone shows that 12 to 14 per cent of the patients have gross hepatic, peritoneal or omental involvement and that only palliative colostomy is justifiable. In the series being reported resection was undertaken even when the palpable hepatic nodules aggregated less than 3 cm. in diameter.

The resectability of the lesions by the method of anterior resection depends on the level of the lesion. For lesions more than 10 cm. from the dentate line the resectability rate was 86 per cent. All resectable lesions at this level were removed by anterior resection. If the lesion was perforating, a part of the abdominal wall or psoas muscles was excised by cautery as necessary. Involvement of the bladder, ureters or small intestine did not prevent resection. For lesions at 10 cm. from the dentate line the resectability rate was 80 per cent and for those at 8 cm. it was 44 per cent. This is the lowest level of general applicability of the operation. At 6 cm. there must be favorable anatomic relations—a thin person with a broad, flat pelvis. It is my opinion that low anterior resection is applicable only rarely when the lesion is situated as low as 6 cm. from the dentate line. There are several alternative methods for handling such lesions. In this region one approaches the point where the allowable 3 cm. of retrograde spread and lateral direct extension involve the lateral efferent lymphatics accompanying the middle hemorrhoidal vessels. Such lesions must be resected by a method which in addition to removing the spread in the pelvic mesocolon allows for resection of (1) the stalks of the middle hemorrhoidal vessels, (2) levator ani muscle with the nodes included between it and the pelvic fascia, (3) the ischiorectal fat and (4) a large part of the perianal skin. One must not apply the pessimistic aphorism that if the lymphatics or veins are involved no operation is radical enough and that if there is no spread of the disease most operations for cancer are too radical.

#### HOSPITAL MORTALITY RATE FOLLOWING ANTERIOR RESECTION

In the 426 cases of anterior resection of lesions between 6 and 20 cm. from the dentate line there were 25 deaths (5.9 per cent). Eighteen of the deaths occurred after the first stage of the operation, the anterior resection, and seven followed closure of the colonic stoma. Seven of the 18 deaths after anterior resection followed peritonitis, two followed pelvic abscess, and each of the following was responsible for a death: coronary occlusion, pulmonary embolus, diabetic acidosis and bronchopneumonia. Of the seven deaths following closure of a colonic stoma, four resulted from peritonitis,

two from pulmonary embolus and one from coronary occlusion. Five of the seven deaths occurred before antibiotics and sulfonamides were employed preoperatively and postoperatively.

The mortality rate from colonic operations has fallen remarkably with the years. For all operations on the colon at the Mayo Clinic in 1934 the mortality rate was 16 per cent. For some reason the rate increased in 1936 and was 22 per cent but during the past four years it has been less than 5 per cent. I attribute a large part of the success in reducing the mortality rate to the use of sulfonamides. Inspection of the figures broken down, to reveal the rates for the sigmoid, rectosigmoid and rectum, will further demonstrate this. From 1907 to 1936 the mortality rates remained nearly constant and those figures are grouped together. The startling improvement

TABLE I.—*Anterior resection 1930-1947: hospital deaths by periods*

Date	Cases	Deaths	
		Number	Per cent
1930-1935 .....	47	4	8.5
1936-1940 .....	109	14	12.8
1941-1947 .....	270	7	2.6
All years .....	426	25	5.9

TABLE II.—*Anterior resection; nonpalliative operations; five-year survival rates for different levels*

Distance from dentate line, cm.	All cases		Nodes not involved		Nodes involved	
	Number	Per cent survival	Cases	Per cent survival	Cases	Per cent survival
6-10 .....	74	63.7	32	72.4	42	57.1
11-15 .....	97	70.2	58	78.8	39	57.7
16-20 .....	101	66.9	60	71.5	41	60.4
All levels .....	272	67.7	150	74.0	122	58.5

has occurred in the resection of sigmoidal lesions. The mortality rate following sigmoidal resection is 8.2 per cent of what it was ten years ago while that of the rectosigmoid is 15 per cent, and of the rectum, 41 per cent of what it was ten years ago. Resection of the rectum which used to be the safest has been improved the least and now operation in that region is carried out with the least safety. The majority of operations for lesions in this segment are combined abdominoperineal procedures. The improvement in rectal surgery occurred at the time of the introduction of the intraperitoneal vaccine and systemic and intraperitoneal administration of sulfonamides. There was no additional improvement from the use of sulfasuxidine. On the other hand, with lesions occurring above the pelvic peritoneal fold, there was a further marked improvement after the introduction of sulfasuxidine. The improved results cannot alone be attributed to vitamins, intravenously administered amino acids, multiple blood transfusions or aseptic anastomosis, since these adjuvants were rarely used in this series of cases.

Table I shows the mortality rates for the operation of anterior resection for three periods. During the years 1936 to 1940 more tissue was excised at the operations than previously and the mortality rate was 12.8 per cent. This mortality rate compares favorably with that for other operations in the same region at the same period. However, in the past seven years, the mortality rate has been reduced to 2.6 per cent.

#### SURVIVAL RATES

In 272 cases the operation was performed sufficiently long ago to provide data for calculating survival rates. Figure 6 shows graphically the survival rate in the 272 cases. After five years 67.7 per cent of the patients were alive; 49.8 per cent were alive after ten years. By the method of calculating survival rates it is impossible to prolong the curve beyond the last death recorded in the series.

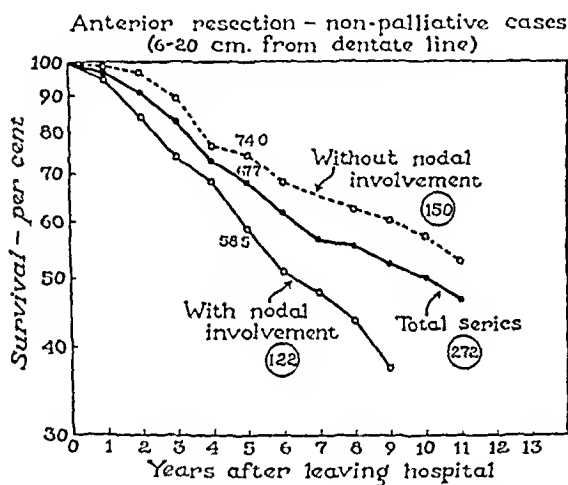


FIG. 6.—Survival rates of 272 cases in which the operation of anterior resection was performed. Palliative operations are omitted. The poorer prognosis in the 122 cases in which the lymph nodes were involved is demonstrated. The five-year survival rates are indicated.

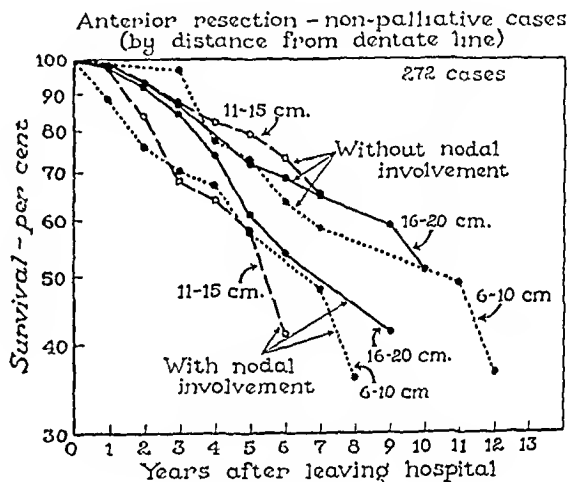


FIG. 7.—Survival rates of the same 272 cases as are included in figure 6. In figure 7, however, the rates are given for the different segments of the rectum and sigmoid in order to show that the operation of anterior resection applied to the upper half of the rectum is not attended by a greater degree of recurrence.

Table II gives the five-year survivals for each level in cases with and without nodal involvement. The best results were obtained from the removal of lesions occurring 11 to 15 cm. from the dentate line. It was hoped to show the effect of the grade of the lesion by breaking down this table but the numbers were too small to be statistically significant. Worthy of mention however are two cases in which the lesion was of grade 4, type C (Dukes). The patients are still alive six years after the resection. The first patient on whom the operation was performed in 1930 is still alive. Figure 7 shows graphically the survival rates for cases with and without nodal involvement divided according to incidence at each level in the bowel. Here again it was necessary to discontinue the curve at the last death in the series.

In 20 of the cases the lesion was of the mucous (colloid) type of adenocarcinoma; 18 patients were dead within three years. One patient lived five years; the other survivor lived nine years. It seems that the mucous type of lesion is rarely amenable to cure by resection. A similar poor prognosis was noted for those cases in which the lesion was of the papillary type, for none of the five patients lived for three years.

In eight cases an asynchronous primary malignant lesion was subsequently removed; in five of these cases the lesions were in the colon and in three they were in the breast. Of the 85 patients who survived operation but died subsequently, the cause of death, according to available data, was obtained either at death, on a return visit to the clinic or from an adequate report from the local physician who was present at the death. In 15 cases there was local recurrence of the disease. In four carcinomatosis was present and in four, intestinal obstruction was responsible for the death. In 20 cases the liver was involved but there was no evidence of local recurrence. Metastasis to the bone was observed in five cases, to the liver and bone in two, and to the lung and bone in two. In 11, the death was from some other cause: cardiac in four, cerebral hemorrhage in three, pneumonia in two, and from an accident in two. The cause of death was not definitely determined in six cases.

Stricture at the site of anastomosis occurred in five cases. This condition was managed by manual dilation in two cases. In two cases exploration was carried out; one required reperformance of colostomy six months after a stoma had been closed. This patient subsequently refused laparotomy to repair the stricture and still depends on the stoma for adequate elimination.

#### SPHINCTERAL CONTROL AND SEXUAL FUNCTION

No change in sphincteral control was observed in any of the cases. In fact, many patients who formerly complained of constipation stated that their intestinal habit had improved.

Although a survey was not made of the sexual function in cases after operation there seemed to be no complaint, other than that eight male patients volunteered that while erection occurred as before there was no emission during ejaculation. In all of these eight cases the lesion was low in the bowel and extensive and it is probable that the seminal vesicles or ducts were detached in the course of the dissection.

#### RELATIONSHIP OF ANTERIOR RESECTION TO OTHER PROCEDURES

When it was found at the exploratory operation that the lesion was too low in the bowel to be removed by anterior resection, colostomy was performed and the lesion removed by posterior resection two to three weeks later, with the patient in prone position. If the patient is in good condition or if there is nodal involvement a single-barreled sigmoidal stoma is provided by bringing the bowel out through a stab wound, the superior hemorrhoidal vessels are ligated and the sutured stump of rectosigmoid is left free in the abdomen.

The blood supply from the middle and inferior hemorrhoidal vessels is adequate to sustain the normal intestine but when posterior resection is carried out approximately two weeks after colostomy it is observed that the lesion has undergone degenerative changes and its vessels are thrombosed. If the patient presents a poor risk, double-barreled sigmoidal colostomy is as much as should be attempted at the time of the exploratory procedure. In such circumstances, at perineal resection, one can ligate the vessels and transect the intestine well up in the abdomen. One does not attempt to remove the rectum as a tube but takes out all of the perirectal tissue en bloc,

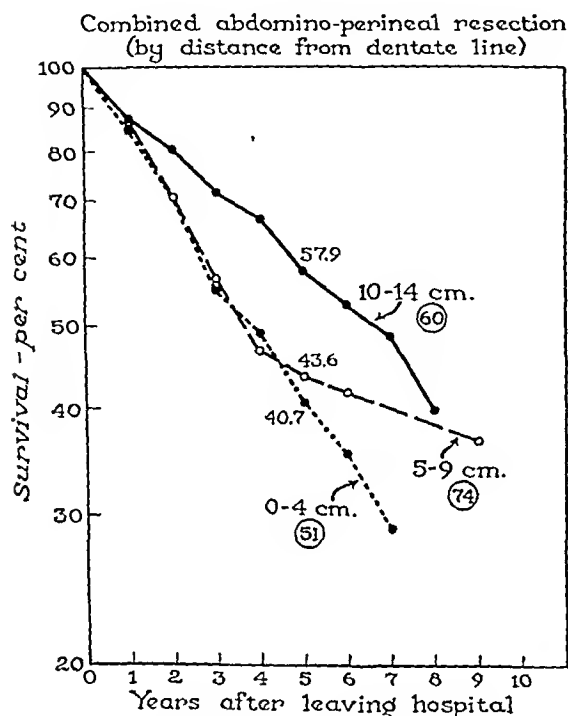


FIG. 8.—Survival rates in 185 cases in which the Miles combined abdomino-perineal resection was applied. The incidence in the various segments is given and the curves show the poorer prognosis after resection of lesions of the lower half of the rectum. The five-year survival rate for each segment is indicated.

often more than the average patient can withstand at one time.

To evaluate this contention I have selected a group of cases in which one-stage combined abdominoperineal resection was carried out during the same time interval as the anterior resections were performed and have divided the cases according to the distance between the lesion and the dentate line (Fig. 8). The series are not strictly comparable with one another but the differences in survivals for the same operation at different levels are comparable. The five-year survival rate for the patients having the lowest lesions, 0 to 4 cm., was 40.7 per cent; for lesions 5 to 9 cm. from the dentate line it was 43.6 per cent, and for those 10 to 14 cm. from the dentate line,

dissecting along the membranous urethra and prostatic capsule, or vaginal wall, as the case may be. The coccyx is removed and the levator ani muscle with its investing fascia and nodes is resected. No procedure really eliminates the lateral spread to the hypogastric nodes but one carries out the most radical excision that is possible.

When performed in the classic fashion<sup>9</sup> the one-stage combined abdominoperineal resection leaves little room for improvement. However, in practice, a poor resection is common in the region of the lesion, while the resection of the pelvic mesocolon is excellent. After spending the major part of the time eliminating the distal spread of the disease the surgeon may merely cone out the rectum itself, ignoring the local lateral efferent lymphatics. A radical abdominal operation and a radical perineal resection are

57.9 per cent. The survival rates in cases in which the lesions were below the pelvic peritoneal fold and in which the combined abdominoperineal resection was employed, are distinctly poorer than those in cases in which the lesion was above the pelvic peritoneal fold. The added incidence of lesions in the lower segment with nodal involvement is not sufficient to account for the difference.

To complete the picture, Figure 9 shows the survival rates in 475 cases of posterior resection performed in the same interval, 1930 to 1944 inclusive. It will be remembered that this operation was carried out when the lesion

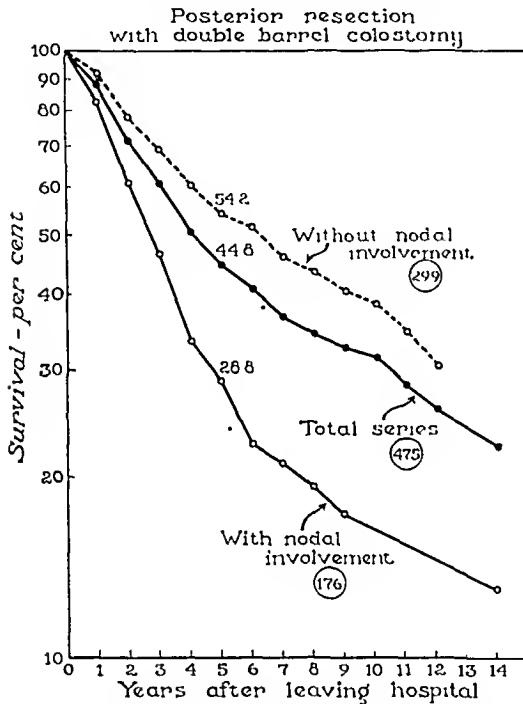


FIG. 9.—Survival rates in 475 cases in which a radical posterior resection was performed. This figure is a complement to figure 7, for these are the cases in which the lesion was too low for performance of the operation of anterior resection. This figure includes the lesions in the distal 6 cm. of rectum plus those occurring up to 10 cm. from the dentate line, in which the lesion was too extensive for anterior resection. The curves show that resection of lesions of the terminal portion of the rectum is attended by a poorer prognosis and that nodal involvement in this region is of graver significance than in cases in which anterior resection could be performed.

cent for cases in which there was nodal involvement as compared with 54.2 per cent for those without nodal involvement shows how much poorer the prognosis is in the presence of lesions of type C (Dukes) in the low rectal region. Carcinoma in this region occupies a very strategic position,

was too low for anterior resection. Therefore, it includes the most extensive lesions at 6 to 8 cm. from the dentate line in addition to all of the lesions below 6 cm. that were encountered in the series. Thus, the group of anterior resections plus this one of posterior resection corresponds roughly to the group of combined abdominoperineal resections.

The five-year survival rate in the series of cases of posterior resection was 44.8 per cent. This operation is considered inadequate by many authors. Yet, when properly carried out, it is much more radical locally than combined abdominoperineal resection and can be as radical along the pelvic meso-colon. The corresponding five year survival rates for the combined operation were, as stated previously, 40.7 per cent for lesions 0 to 4 cm. and 43.6 per cent for lesions 5 to 9 cm. from the dentate line. Figure 9 also gives the survival rates for posterior resection, divided according to lesions with and without nodal involvement. The five-year survival rate of 28.8 per

straddling the anastomosis between the portal and systemic venous systems. In addition the spread that takes place along the lateral efferent lymphatics accompanying middle and inferior hemorrhoidal vessels, along the sacral and internal iliac nodes and along the base of the broad ligaments in the female, makes attempts to extirpate the lesion discouraging indeed. In practice, resection of the node-bearing tissue between the pelvic fascia and pelvic peritoneum is usually inadequate. The operation of abdominoperineal proctosigmoidectomy is deficient in these respects and also fails to excise sufficient perianal tissue.

#### SUMMARY

Anterior resection for removal of carcinomas of the upper part of the rectum and lower part of the sigmoid was performed in 426 cases from 1930 through 1947. While there is a slight predominance of males in the series, the female patients tend to be younger and their lesions tend to be of higher grade and closer to the dentate line. There were 25 deaths among the 426 cases, giving a mortality rate of 5.9 per cent. In 270 resections since the present method of preoperative and postoperative management has been used there were 7 deaths (2.6 per cent). Of 272 patients, the five-year survival rate was 67.7 per cent. Comparisons of the mortality and survival rates according to the location of the lesions in various segments of the bowel revealed that the operation is sufficiently safe and radical for lesions of the upper half of the rectum. In cases of adenocarcinoma of the mucous (colloid) and papillary types the prognosis is poorer. The signal improvement in the operative mortality rate in colonic surgery in the past ten years has not been as marked for lesions in the rectum as immediately above that region. Whereas, ten years ago operations for rectal lesions were safest, this no longer is true. The survival rate after resection of low rectal lesions is poorer than that following resection of lesions higher in the bowel. This results from the increase of nodal involvement and greater difficulty in resecting the region of spread. The lesions covered by this study are considered in terms of their distance from the dentate line because of the foregoing consideration and because the possibility of saving the sphincter is determined by this distance.

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# THE SIGNIFICANCE OF THE PROTEIN-BOUND BLOOD IODINE IN PATIENTS WITH HYPERTHYROIDISM\*

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ONCE THE CLINICAL PICTURE of hyperthyroidism becomes manifest in association with nodular or diffuse hyperplastic goiter (with or without exophthalmos) the diagnosis soon becomes apparent. Nevertheless, when thyroid enlargement is not prominent, when complicating and even confusing factors are present, and when the symptomatology exhibited is minimal, a true clinical evaluation of thyroid function often becomes difficult. This problem is particularly pertinent in those regions where goiter is endemic.

In Central Ohio, which lies within the "goiter belt", nodular goiter is frequent; moreover, these patients, at times, have *non-thyroid hypermetabolic diseases* which cause them to have elevated basal metabolic rates and even to present symptoms suggestive of hyperthyroidism. Essential hypertension and varying degrees of cardiac failure are frequently found in association with nodular goiter. Thyroidectomy, undertaken when such complicating diseases are not clearly differentiated and under optimum control may prove disappointing. Various psychiatric disturbances, and particularly anxiety states, present interesting diagnostic problems when nodular goiter is also present. Symptoms arising in association with the menopausal syndrome are of similar concern. Frequently the basal metabolic rate is elevated in those suffering with carcinoma or similar hyperplastic neoplastic diseases, such as the leukemias.

Much of the confusion encountered in making a diagnosis of so-called "borderline" hyperthyroidism has arisen because there have been developed but few direct objective methods for measuring thyroid function itself. The BMR is a measure of oxygen consumption, the end result of a great many oxidative processes, and not necessarily of that alone associated with the transport, utilization and breakdown of the thyroid hormone. Since the thyroid gland is so intimately related to the metabolism of iodine, numerous studies have been made in an attempt to correlate the amount of iodine in the blood with the BMR in patients with thyroid disease. It was soon learned that the total blood iodine was labile and also varied directly with the iodine intake. Consequently, more recent investigation in this field has dealt largely with the protein-bound fraction of the whole-blood, plasma or serum iodine. Our methods for the acetone separation of the whole-blood iodine into protein-bound and inorganic fractions have been presented.<sup>1, 2, 3, 10</sup>

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\* Aided by a Grant from the Comly Fund for Research of the Ohio State University.

\* Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

THE PROTEIN-BOUND (ACETONE INSOLUBLE) BLOOD IODINE  
AS AN INDEX OF THYROID FUNCTION

Two necessary qualifications which any blood iodine fraction should possess in order to represent a satisfactory index of thyroid function, are: *first*, that it should increase along with the BMR following the administration of thyroid-stimulating hormone; and, *second*, that it should decrease along with the BMR when elaboration of the thyroid hormone is blocked by means of goitrogenic agents such as propyl thiouracil.

Figure 1 illustrates the response of the BMR and the protein-bound blood iodine\* to the administration of thyroid-stimulating hormone in man. The

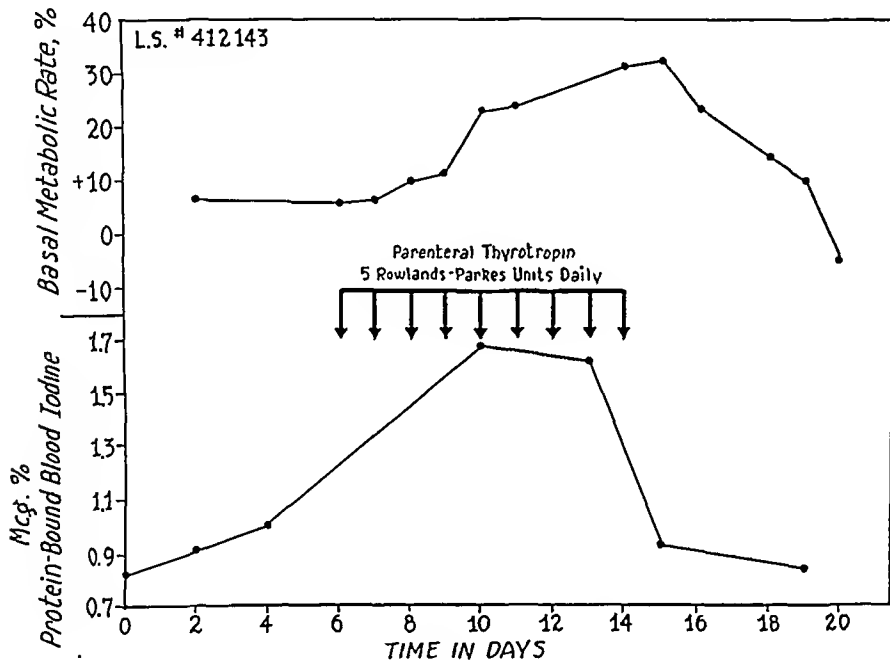


FIG. 1.—Response of the protein-bound blood iodine and of the basal metabolic rate to thyroid stimulating hormone.

peak of the PBI is reached following 5 days of thyroid-stimulating hormone therapy after which it decreases. Characteristically, the BMR rises at a somewhat slower rate, reaching its peak on the 10th day, after which it slowly declines. The decrease of the PBI on the 5th day is illustrative of the refractory response to thyroid-stimulating hormone. Hertz and Roberts<sup>4</sup> found that following thyroid-stimulating hormone administration to the rabbit, the BMR rose to its maximum level on the eighth day of therapy. Our findings in man are similar.

Following Astwood's introduction of thiouracil as a chemotherapeutic agent to block the production of thyroid hormone,<sup>5</sup> many problems in thyroid

\* Referred to hereafter as PBI.

physiology were again investigated. By preventing the manufacture of thyroid hormone presumably by blockade of one or more enzyme systems within the thyroid cell, thiouracil administration is followed by an attendant decrease in the PBI and BMR. The literature concerning the experimental data pertaining to the role of thiouracil and its allies in the treatment of hyperthyroidism has recently been critically analyzed.<sup>6</sup> It is the conclusion of qualified observers that the PBI decreases following administration of those goitrogenic agents.

Figure 2 demonstrates the usual response of the PBI to propyl thiouracil in a patient presenting diffuse hyperplastic goiter with hyperthyroidism. Note the initial decline of both BMR and PBI. Each successive cycle during goitrogen therapy is separated from its predecessor by a greater interval of time. The response of the BMR and PBI are essentially the same in toxic nodular goiter.

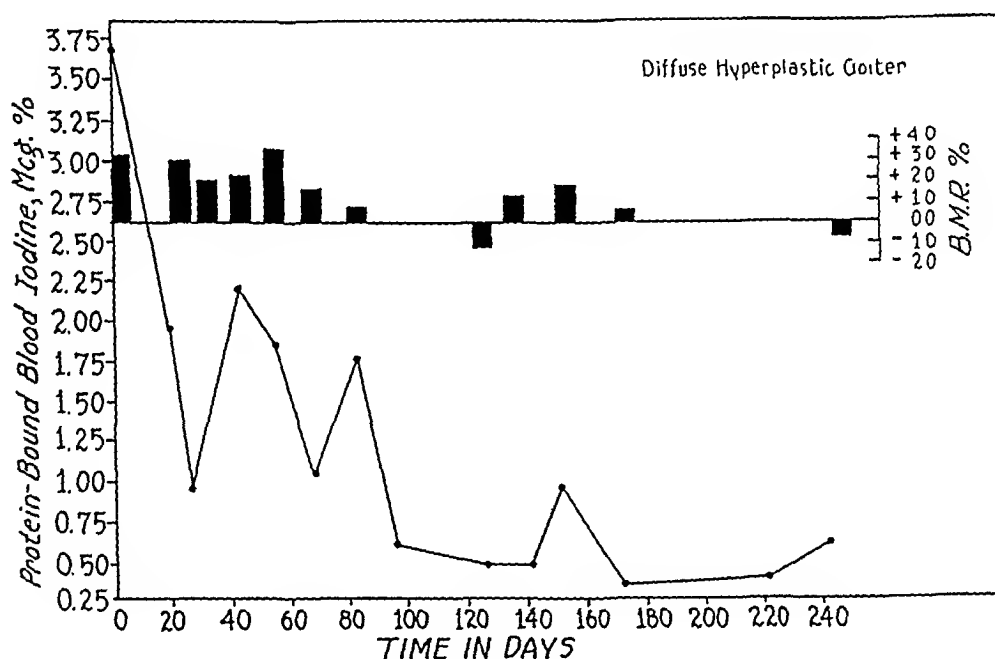


FIG. 2.—Response of the protein-bound fraction of the blood-iodine and of the basal metabolic rate to the administration of 200 mg. cyclopropylthiouracil daily (E.M. at K. H.).

On the basis of studies similar to these we have concluded that the PBI increases characteristically following the administration of thyroid-stimulating hormone and conversely decreases when thyroid hormone formation is blocked by the thiouracil-like drugs. Thus, the PBI may be regarded as a clinical index of thyroid function. Moreover, when the iodoprotein normally occurring in the human thyroid gland, normal human thyroglobulin, is added to normal human serum, and this serum is then fractionated with acetone, the thyroglobulin is quantitatively recovered in the protein-bound fraction.<sup>7</sup>

Previous studies have ascertained that the average normal BMR for the region of Central Ohio is minus 5 plus or minus 8 per cent.<sup>8</sup> Similarly the

average normal total blood iodine concentration equals 4.2 plus or minus 1.2 mcg. per cent.<sup>9</sup> The average normal protein-bound blood iodine (acetone insoluble) is 0.88 plus or minus 0.2 mcg. per cent.<sup>10</sup> This fraction is significantly decreased in patients with hypothyroidism.<sup>10</sup>

We have recently correlated the relations of the PBI and BMR with those symptoms suggestive of hyperthyroidism occurring in 178 consecutive patients with nontoxic nodular goiter.<sup>11, 12, 13</sup> The PBI increases progressively from 0.51 mcg. per cent in those with basal metabolic rates below minus 21 per cent to 1.32 mcg. per cent in those exhibiting basal metabolic rates above plus eleven per cent. Moreover there is a significant *linear* relation between the BMR and the PBI. 66.8 per cent of our patients presented symptoms

TABLE I.—*Toxic Nodular Goiter*

<i>Distribution of patients according to standard deviations of the basal metabolic rate and the protein-bound blood iodine</i>							
(Average Normal BMR = minus 5 $\pm$ 8%. Average Protein-Bound Blood Iodine* = 0.88 $\pm$ 0.2 Mcg. per cent)							
BMR %	+3 to +11	+11 to +19	+19 to +27	+27 to +35	+35 to +43	+43 to +59	Above +59
PBI* Mcg. % ...	1.27	1.65	1.85	1.94	2.16	2.46	3.33
No. of Patients in each Basal Group..	14	12	16	26	17	19	10
% of each Group with PBI above 0.88 Mcg. % .....	85.7	100	100	100	100	100	100
% of each group with symptoms ....	93	91	100	96.1	100	84.2	90
% of each group with PBI above 1.08 Mcg. % the upper Normal limit .....	57.1	100	93.7	92.3	90	100	100

\* PBI = Protein-Bound Blood Iodine

suggestive of hyperthyroidism and of these 70 per cent had elevations of the PBI while only 47 per cent had elevations of the BMR. Consequently, we concluded that the PBI is a better index of thyroid function than the BMR alone.

Symptoms suggestive of hyperthyroidism, listed according to their positive correlations to an elevated PBI, are a pulse of 90 or more per minute, palpitation, weight loss, weakness, nervousness and emotional instability. Patients with nodular goiter in the region of Central Ohio having either (a) a BMR of plus 3 per cent or above and a PBI of 1.2 mcg. per cent or above, or (b) symptomatology suggestive of hyperthyroidism and a PBI of 1.2 mcg. per cent or above, appear to be potentially hyperthyroid.<sup>11, 12, 13</sup>

Hypertension, organic heart disease, neurocirculatory asthenia, anxiety states as well as other psychoneuroses, neoplastic diseases and certain other endocrine disturbances such as acromegaly and adreno-cortical disturbance, may mimic hyperthyroidism.<sup>14-19</sup> By using the PBI as a diagnostic aid it becomes possible to differentiate the hypermetabolism (elevated BMR, but euthyroid) exhibited by the above conditions from true hyperthyroidism.

In hyperthyroidism, the PBI will as a rule be elevated, but in the hypermetabolic states the PBI will be normal or even below, unless hyperthyroidism is also present. Rose<sup>20</sup> has emphasized that hyperthyroidism may be associated with basal metabolic rates consistently within normal limits. The use of the PBI in evaluating the problem which this raises has been discussed,<sup>13</sup> while the presence of hyperthyroidism may be detected by the criteria previously mentioned.

THE PROTEIN-BOUND BLOOD IODINE IN PATIENTS WITH  
TOXIC NODULAR GOITER

Other investigators agree that the protein-bound blood or serum iodine is elevated in hyperthyroidism.<sup>21, 22, 23</sup> Using 114 patients with untreated,

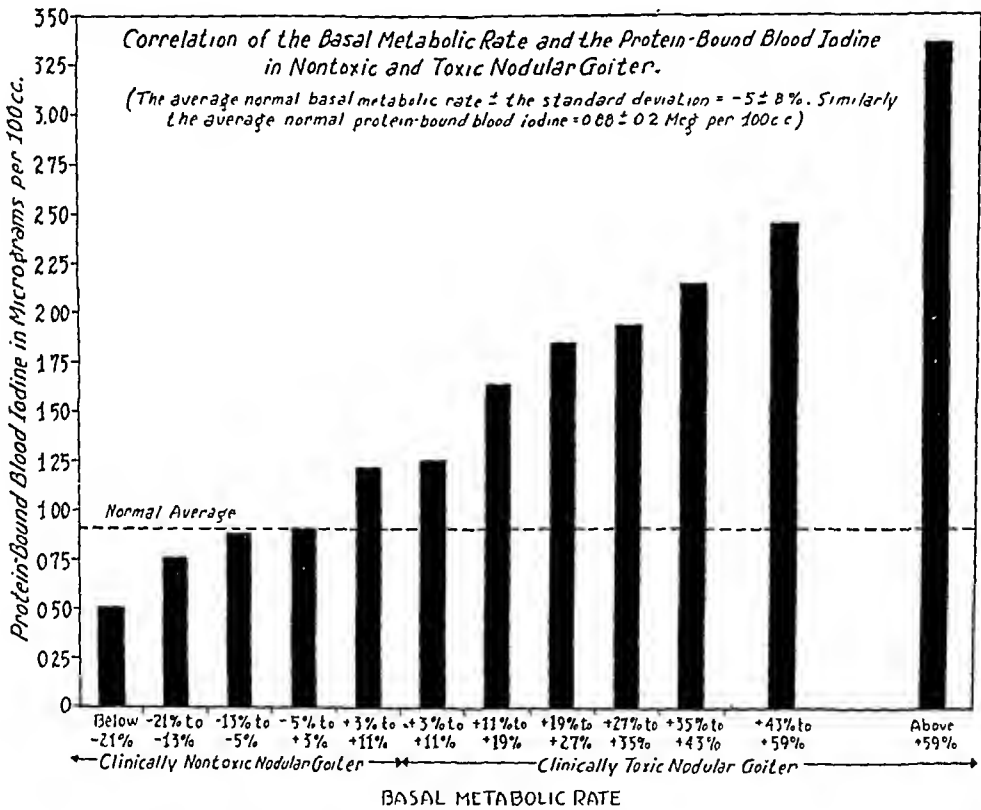


FIG. 3.

uncomplicated, clinically toxic nodular goiter, a detailed correlation of the PBI and BMR has been made and is here presented.

Table I summarizes the distribution of the 114 patients according to standard deviations\* from the average normal BMR. The average PBI progressively increases from 1.27 mcg. per cent in those having basal metabolic rates between plus 3 and plus 11 per cent to 3.33 mcg. per cent in those having basal metabolic rates above plus 59 per cent. A comparison of these

\* The average normal BMR is minus 5 plus or minus 8 per cent, i.e. the standard deviation is 8 per cent.

data with those previously found for nontoxic nodular goiter<sup>11, 12</sup> is presented in Figure 3. The five black bars at the left of the graph illustrate the relation of the BMR to the PBI in nontoxic nodular goiter, while the remaining bars to the right portray a similar relationship for nodular goiter with hyperthyroidism.

A significant, parallel, linear relationship exists between the PBI and the BMR in toxic nodular goiter as well as in the nontoxic type. However, there is considerable overlapping of the clinical diagnosis (either toxic or nontoxic) when the BMR ranges between plus 3 and plus 11 per cent. Consequently, the average PBI of patients having such basal metabolic rates and clinically judged to be nontoxic was compared to a similar group clinically

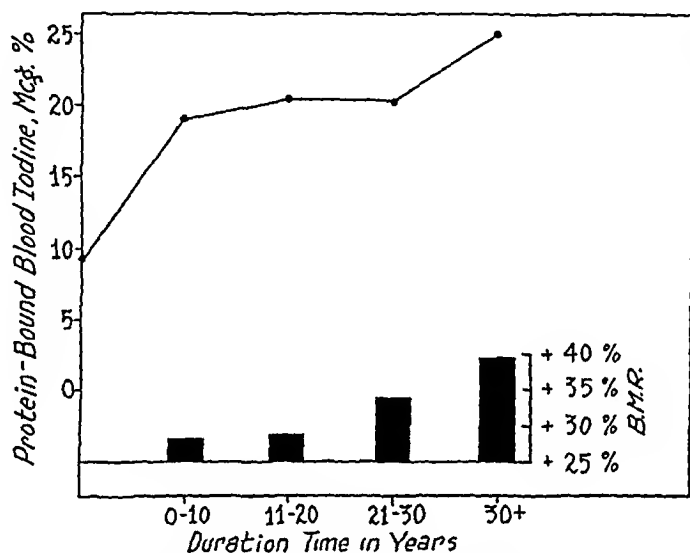


FIG. 4.—Toxic nodular goiter. The basal metabolic rate and the protein-bound blood iodine for each ten year period of goiter duration.

judged to be hyperthyroid. In the former group, the average PBI was 1.21 mcg. per cent, while in the latter it was 1.27 mcg. per cent. The difference was thus less than that of the experimental error. This subtle development of hyperthyroidism in association with the so-called 'harmless goiter' has long been suspected<sup>24</sup> and is here unmasked by determinations of the protein-bound blood iodine. Confusion arising in making a diagnosis upon such patients will be diminished if the significant symptomatology found is correlated with an elevated protein-bound blood iodine.

Further evidence that toxic nodular goiter develops as a sequel to its nontoxic predecessor is found in the correlation between the duration of the goiter, the PBI and the BMR, Fig. 4. The average PBI increases from 1.86 mcg. per cent during the 0-10 year period to 2.50 mcg. per cent in those having had goiter for 30 or more years. In nontoxic nodular goiter patients a similar tendency for the PBI to increase with the duration of goiter is also present.<sup>12, 13</sup>

A significant per cent of the symptomatology suggestive of hyperthyroidism presented by patients with nontoxic nodular goiter has been found to be associated with a BMR of plus 3 per cent or above and with a PBI of 1.2 mcg. per cent or above.<sup>12, 13</sup> Of the 114 untreated, uncomplicated patients with toxic nodular goiter 91.2 per cent had PBI levels above the normal average of 0.88 mcg. per cent, while 89.4 per cent had levels above the upper limit of normal (1.08 mcg. per cent). Symptoms suggestive of hyperthyroidism were exhibited by 93.8 per cent of the entire group.

TABLE II.—Diffuse Hyperplastic Goiter.

Distribution according to two S. D. limits of the basal metabolic rate and correlation with the protein-bound blood iodine							
BMR %	-5 to +3%	+3 to +19%	+19 to +35%	+35 to +51%	+51 to +67%	+67 to +83%	Above +83%
No. of Patients in each group..	4	13	22	16	14	13	8
Average PBI Mcg. % .....	1.53	1.96	2.07	2.10	2.98	3.15	3.38
% of each group with one or more symptoms of Hyperthyroidism	100	100	100	100	100	100	100

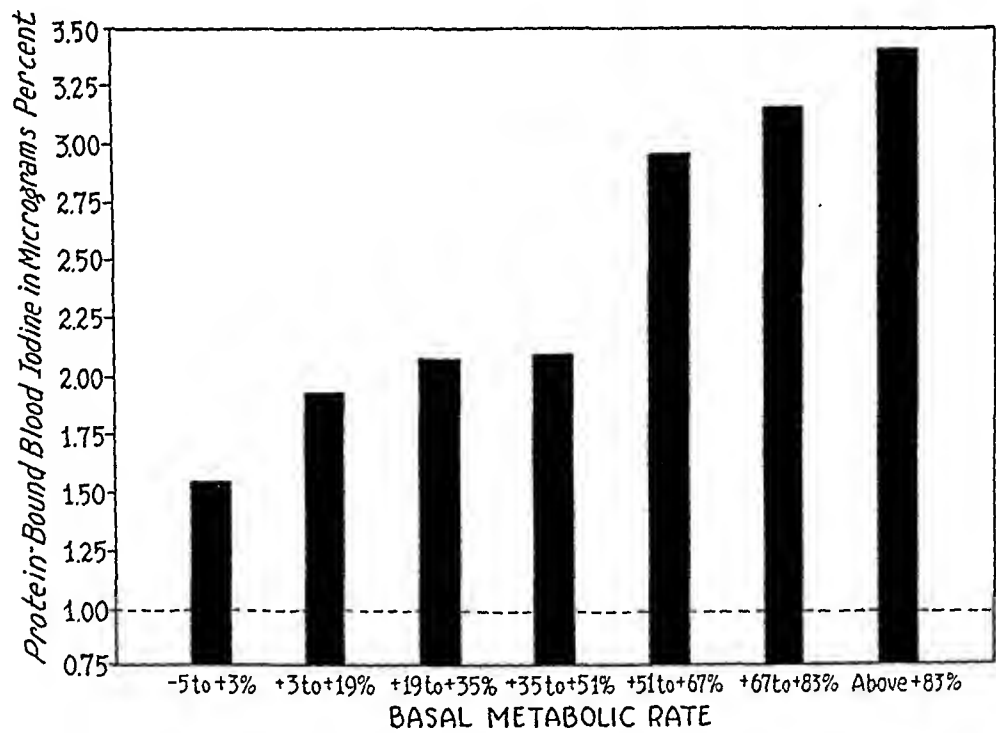


FIG. 5.—Diffuse hyperplastic goiter. Correlation of the basal metabolic rate and the protein-bound blood iodine (The average basal metabolic rate  $\pm$  the standard deviation =  $5 \pm 8\%$ . Similarly the average normal protein-bound blood iodine =  $0.88 \pm 0.2$  micrograms per cent.).

THE PROTEIN-BOUND BLOOD IODINE IN PATIENTS WITH DIFFUSE  
HYPERPLASTIC GOITER WITH HYPERTHYROIDISM

For the purposes of this paper, *primary* hyperthyroidism is defined as hyperthyroidism associated with diffuse hyperplastic goiter with or without



exophthalmos. Ninety consecutive patients with untreated, uncomplicated primary hyperthyroidism have been studied.

Table II summarizes the distribution of the 90 patients according to two standard deviations of the BMR and further lists the average PBI for each basal group. The PBI progressively increases from 1.53 mcg. per cent in the minus 5 to plus 3 per cent basal group to 3.38 mcg. per cent in the group having basal metabolic rates above plus 83 per cent, Fig. 5. It is striking that within the upper normal BMR range (minus 5 to plus 3 per cent) the PBI average is almost twice normal.

In general, (compare Table I with Table II) the average PBI levels for the various basal groups of those with primary hyperthyroidism are higher than for the similar groups having nodular goiter with hyperthyroidism. This presumably indicates a more severe type of hyperthyroidism. As a consequence, the incidence of symptoms is higher. *All* of the patients with diffuse hyperplastic goiter with hyperthyroidism presented one or more

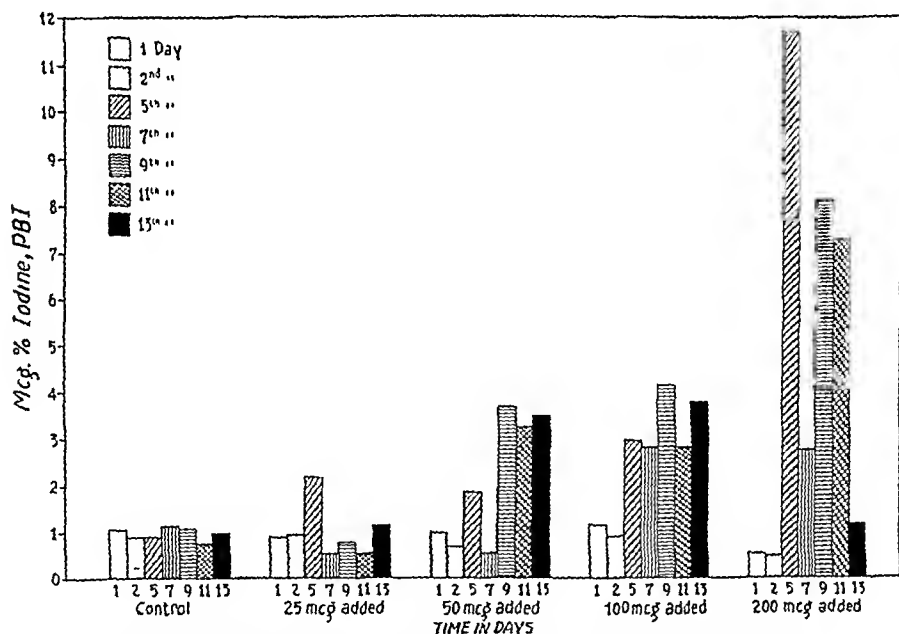


FIG. 6.—Effect of increasing amounts of iodine, added as potassium iodide, upon the protein-bound fraction of the blood iodine.

suggestive symptoms. A linear relationship between the PBI and the BMR also exists in primary hyperthyroidism, but at a higher level than that found for toxic nodular goiter.

Of those with hyperthyroidism associated with nodular goiter, 93.8 per cent presented symptoms; of those with diffuse hyperplastic goiter with hyperthyroidism, 100 per cent presented symptoms. However, there is a greater incidence of symptoms in the primary type of hyperthyroidism than is apparent by comparing only the number of patients with symptoms. Data pertaining to correlation of the PBI with the symptomatology will be presented elsewhere.

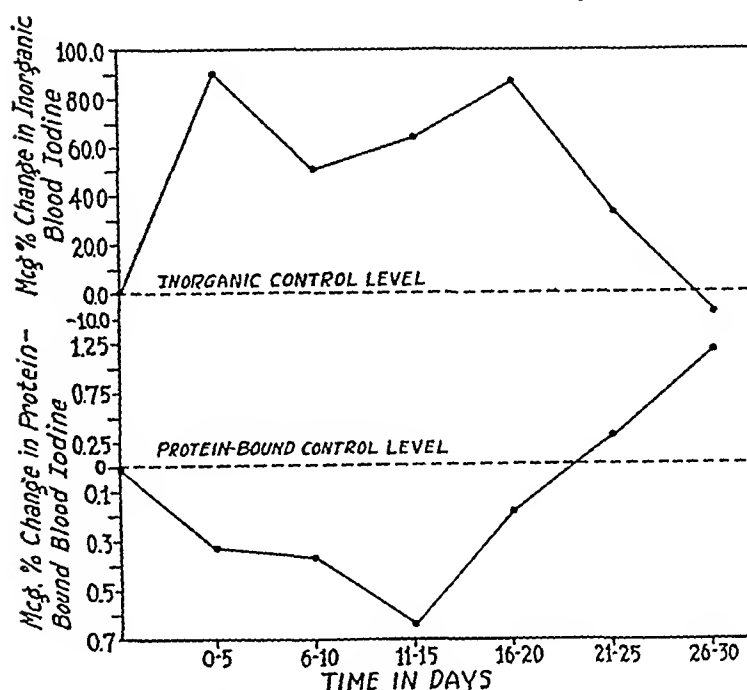


FIG. 7.—Diffuse hyperplastic goiter. Micrograms per cent change in the blood iodine fractions following iodine administration, 100 Mg. daily as potassium iodide.

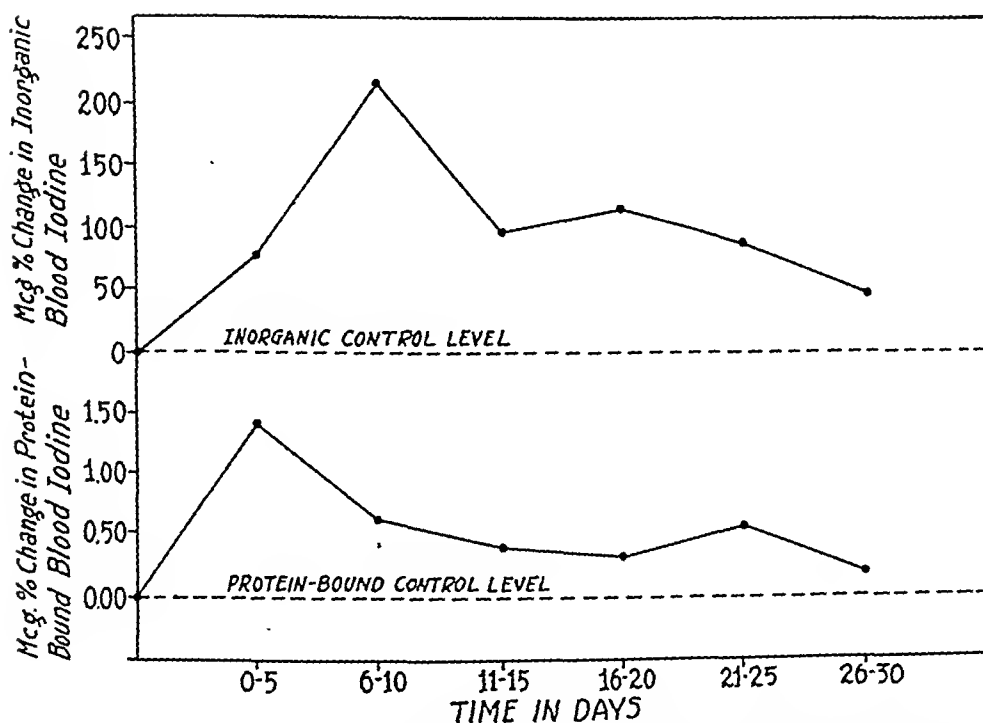


FIG. 8.—Toxic nodular goiter. Micrograms per cent change in the blood iodine fractions following iodine administration, 100 mg. daily as potassium iodide.

RESPONSE OF THE INCREASED PROTEIN-BOUND BLOOD IODINE  
IN HYPERTHYROIDISM TO CONTINUED IODINE THERAPY

Many investigators have studied the varying phases of the iodoproteins.<sup>25-30</sup> Thyroxine has been isolated from artificially iodinated casein, and optimum results were obtained when four atoms of iodine per molecule of tyrosine were added.<sup>31, 32, 33</sup> Similarly, thyroxine-like and diiodotyrosine-like peptides have been isolated from iodoproteins prepared from serum proteins *in vitro*.<sup>29</sup> The Schardinger enzyme may be intimately concerned with such biologic iodinations.<sup>34</sup>

Following iodine therapy of hyperthyroidism, Salter noted 'spurious' elevation of the protein-bound serum iodine but thought it a chemical artefact; however, he reproduced the phenomenon *in vitro*.<sup>39, 40</sup> In order to determine the relation of such a type of protein iodination to the PBI, we have added varying amounts of potassium iodide to human whole-blood *in vitro*. Fractionation with acetone was then carried out after varying intervals of time.

Figure 6 demonstrates that but little iodination of protein occurs following this procedure, until the total iodine concentration reaches 100 mcg. per cent; further, a striking increase in the protein-bound fraction occurs on the fifth day, strongly suggestive that the reaction at first proceeds according to a 'lag phase' and then by a 'log phase.' This lends support to the premise<sup>34</sup> that certain enzymes play a role in such iodinations.

When the average response of the PBI to continued iodine therapy in primary hyperthyroidism is compared to that of toxic nodular goiter, a striking difference becomes apparent. The average response in primary hyperthyroidism, Fig. 7, is in accordance with the present accepted concepts of the mechanisms of the iodine-induced remission in hyperthyroidism. It is likely that iodine inactivates thyrotropin<sup>35</sup> and temporarily inactivates enzyme systems releasing thyroid hormone from the thyroid follicles.<sup>36, 37</sup> The average response in toxic nodular goiter Fig. 8, mirrors the level of the inorganic blood iodine, and is similar to the response noted following the *in vitro* addition of potassium iodide to blood. *It is difficult to explain these variances unless fundamental differences in tyrosine metabolism, diiodotyrosine and thyroxine turnover and thyroglobulin metabolism exist between the two types of hyperthyroidism.*

Taurog and Chaikoff<sup>38</sup> have reported that following iodine administration to rats, the level of the protein-bound plasma iodine is dependent upon the thyroxine content of the thyroid gland, and is limited by the capacity of the thyroid to produce thyroxine. Our data indicate that the iodination of protein may occur within the blood itself.

## SUMMARY AND CONCLUSIONS

1. The protein-bound (acetone-insoluble) blood iodine is presumably thyroglobulin-like in nature.

2. The PBI increases following the administration of thyroid-stimulating hormone to man; conversely, it decreases when thyroid function is blocked by administration of the goitrogenic drugs. It thus becomes a clinical measure of thyroid function.

3. There is a progressive linear relation between the BMR and the PBI in uncomplicated nodular goiter. Determination of this relation unmasks the development of hyperthyroidism in previously quiescent nodular goiters.

4. Hyperthyroidism is probably associated with nodular goiter in Central Ohio once the BMR exceeds plus 3 per cent and the PBI exceeds 1.2 mcg. per cent, or when suggestive symptoms are present and the PBI exceeds 1.2 mcg. per cent.

5. The criteria of conclusions 3 and 4 provide a diagnostic aid for measuring the onset of hyperthyroidism, and for differentiating early hyperthyroidism from other diseases mimicking it.

6. A linear correlation exists between the PBI and BMR in primary hyperthyroidism, but at a higher level than in toxic nodular goiter.

7. Symptoms presented in hyperthyroidism have been correlated with the PBI and the BMR. The incidence of all symptoms in primary hyperthyroidism was 67.1 per cent more frequent than in toxic nodular goiter in the group of patients studied.

8. After iodide therapy, the average response of the PBI in primary hyperthyroidism differs from that of toxic nodular goiter. In the former, the average response follows well established lines, while in the latter the response parallels that noted following the addition of iodide to whole blood *in vitro*. The significance of this finding is uncertain.

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DISCUSSION.—DR. FRANK H. LAHEY, Boston: This is a fine demonstration of the value of blood iodine studies, particularly in doubtful cases. I discussed a paper of Dr. Curtis' similar to this, a short time ago, and in it have said that if one has a research laboratory such as he has and we have, concerned with the study of blood iodine, then these methods are readily available. Blood iodine studies are, however, time-consuming, they are expensive and they are open to a great possibility of error. For that reason I wish to present another method of separating patients with falsely elevated metabolisms and those with truly elevated metabolisms. Dr. Elmer C. Bartels, of the medical department of the Clinic, has developed this method. He has shown that if patients with falsely elevated metabolic rates are placed under pentothal anesthesia, such a metabolism can then be demonstrated to be at a truly normal level. He has also shown by doing metabolisms on patients with known normal basal metabolic rate, that during the determination under pentothal, there is no elevation of the basal rates. This is a valuable method to employ in the doubtful case in which the basal rate is persistently elevated but the patient lacks the clinical evidences of hyperthyroidism to go with it.

# DORSAL CORDOTOMY FOR PAINFUL PHANTOM LIMB\*

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FOLLOWING THE AMPUTATION of a major portion of an extremity the patient usually experiences the sensation that the missing part is still present. This has been aptly termed phantom limb. In most instances, the ghost part is not particularly bothersome and adaptation to the new body pattern ensues within a few months after the amputation. In some, however, the phantom becomes the source of considerable distress or even intractable pain. Although the ghost is seldom a precise replica of the amputated part, it often bears a strong resemblance to it. Some patients describe the phantom as a small hand or foot attached to the end of the stump of an arm or thigh, without intervening forearm or leg. In others, the false image assumes an unalterable distorted posture and may be the source of continuous cramp-like pain. Various descriptions of the phantom are given by patients and in some it is logical to attribute the complaints to stump neuromas or causalgia.

It does not seem at all surprising that there is a perpetuation of the patient's concept of his own body image after the sudden removal of or somatic denervation of a part. Each individual in the process of growth and maturation comes to appreciate a normal body pattern for himself. If he were born without an extremity there would not be a phantom of the missing part since it was never included in the normal body pattern. In other words, that which he had never had would not be missed. This we have found to be the case. Considering one's ability to adjust psychologically as well as physiologically to altered body patterns, it is readily understandable that a phantom of a part removed persists for a period following its removal. After weeks, months, or in a few years, this phantom gradually recedes from the conscious state but sometimes it can be recalled, as expressed by one patient who sustained a traumatic amputation some 50 years before. "I can always call it (the phantom) back by thinking about it". Moreover, the prominence of the hand or foot in the phantom may be logically explained by the anatomic fact that these parts have a much greater cerebral representation than the forearm and leg. Be that as it may, our critical interest in phantom limb stemmed from our unsuccessful attempts to treat patients with cramp-like pain allegedly due to an unalterable posture of the phantom hand or foot. After running the gamut of sympathetic ganglionectomy, rhizotomy and anterolateral cordotomy in a somewhat empirical manner and without success, it occurred to us that possibly division of a part or all of the dorsal

column of the spinal cord on the side of the phantom might deprive the patient of a knowledge of the position of the ghost part and thereby eliminate the pain.

From our limited experience up to this point it was evident that patients with phantom limb presented a great variety of complaints. Success had followed the first dorsal cordotomy, but our knowledge of the problem was too meager and the available recorded information so vague that a critical analysis of the subject seemed indicated before proper selection of patients for this operation could be made. It was therefore decided to study a series of patients of variable age who had for one reason or another lost an extremity or extremities either by accident or by elective surgical amputation. Ample material as to numbers was available at the Kings County Hospital; however, the majority of the patients in this institution subjected to major amputation were in the fifth and sixth decades of life and the extremity or extremities had been amputated for some sort of primary vascular disease. We were most fortunate to have placed at our disposal by Dr. George Deaver, patients undergoing rehabilitation at the Institute for Crippled and Disabled, New York City, since here were found an intelligent group coming from many walks of life. The amputations had been performed from a few months to several years prior to interrogation. In addition to the material from the Kings County Hospital and that studied at Doctor Deaver's clinic, a group of individuals born without extremities were questioned and the results included in this series.

Altogether there were 150 subjects, 137 with surgical amputations and 13 born without one or more extremities. Among the 137 patients comprising the surgical group, 159 extremities had been amputated. There were 115 with a major part of a single extremity absent and 22 with multiple amputations. Patients with language difficulties due to foreign birth and those with intellectual alterations interpreted as the result of senile changes were excluded as unfit for study. Included in the series were lawyers, physicians, dentists, artists, school teachers, laboratory technicians, mechanics and laborers. A detailed description of the phantom part was obtained from each and the stump was carefully examined in every case. Eighty-two patients in the surgical group had lost the extremity two or more years prior to the time of the examination. All of these patients were self-supporting and well adjusted to their handicaps. Thirty-three others had been subjected to amputation from six months to two years prior to the present study. Many of the patients in this category were still in a stage of physical rehabilitation, although complete healing of the stump had occurred in all. The remaining 22 patients comprised those with relatively recent amputations. In the majority of these the extremity had been removed only a few weeks prior to this study and in many, complete healing of the amputation site had not occurred. The reason for absence of the extremities is shown in Table I.



## CONGENITAL ABSENCE OF AN EXTREMITY OR EXTREMITIES

There were 13 subjects in the series born without the whole or a major part of one or more extremities, a total of 17 missing extremities occurring in this particular group. In 11 of the subjects part of one or both upper extremities was missing, in one an entire lower extremity and in the remaining subject a major portion of both upper extremities as well as a part of a lower extremity were absent. Phantom-limb had never been present among any of these although such a phenomenon was well known to several of them.

## PHANTOM OF THE UPPER EXTREMITY

The most striking examples of phantom limb occur after the removal of all or a major part of an upper extremity. Usually the description given by these patients is far more elaborate and vivid than that after a loss involving the lower extremity. The sensory ghost is often present continuously for many years and in some shows practically no tendency to disappear.

TABLE I.—*Reasons for Absence of Extremities*  
150 Patients

Congenital absence .....	13
Occlusive vascular disease.....	70
Traumatic severance .....	44
Primary infection .....	14
Extensive burn .....	3
Congenital deformity .....	3
New growth .....	3

A total of 19 surgical amputations of the upper extremity were studied and phantom limb was present in 17 instances. The amputation had been performed above the elbow in nine and below the elbow in ten. Three of the 19 had sustained accidents that required amputation during infancy. A typical example of the syndrome of phantom limb as it occurs following the loss of an upper extremity is illustrated by the following history.

C. T., a 51-year-old physician, was wounded in the right elbow by a charge of buckshot while on a hunting trip in Mexico. The lower arm and elbow were avulsed leaving the distal part hanging by a few shreds of tissue. There was no loss of consciousness. There was severe pain in the shattered part. Some twelve hours after injury the damaged extremity was amputated four inches below the shoulder. Directly after awakening from the anesthesia there was felt a phantom forearm and hand. The forearm seemed to be flexed and internally rotated while the hand was extended at the wrist. The fingers were held in extension and pursed together at their tips. The ghost hand appeared to be situated near the elbow with the forearm shortened. The hand, especially the fingers, was described as being the outstanding part of the phantom. The fingers could be "moved" without difficulty but usually they remained straightened out and pressed together. The entire hand felt uncomfortable and heavy as though it were immersed in mercury. Our examination was

carried out one year after the amputation. No change in the phantom limb had occurred during this period.

Usually upon recovery from the anesthetic or within a day, regardless of the level of amputation (through the forearm, arm or at the shoulder joint) there was felt a phantom hand and wrist that seemed to be in the region of the end of the stump but not necessarily attached to the stump. Occasionally parts of the missing forearm, elbow or distal arm were included in the phantom. In one instance the entire missing upper extremity was represented in the ghost. In several, the thumb and index finger were prominent parts but the remaining fingers, the palm, back of the hand and the wrist, while present, were not as vividly represented. In seven of the 19 the phantom felt "like a doll's hand or a baby's hand". In only one of these seven had the extremity been amputated during childhood. In 12 the fingers of the phantom were perceived as closed in a tight fist. In three others, the ghost hand was continuously open but the fingers were firmly pressed together and could not be separated. In one the thumb and index finger were flexed toward each other as though a small object was being held between them. Several of these variable features were disclosed in a single subject.

This unusual and often distorted posture of the phantom part has been commented on by several observers, notably Riddoch.<sup>1</sup> It has been stated that the posture that persists in the ghost represents the last remembered position of the limb prior to its removal. Six of this group could recall with accuracy the precise position of the hand and forearm just before being given an anesthetic for amputation and in only one did the posture of the phantom bear any resemblance to that of the extremity just before amputation. This patient was an 18-year-old male who lost his entire hand by the accidental explosion of a blasting cap which he was holding between the thumb and index finger. The phantom hand, as mentioned above, was felt as if the thumb and index finger were almost approximated and he were still holding the blasting cap but the cap could not be felt between them. The fingers of the ghost have remained fixed in that position for almost three years.

Quite in accordance with the statements that we have made regarding body pattern, is that concerning the perpetuation of a deformity in a phantom. That is, after the amputation of an abnormal extremity, a long-standing deformity will be a part of the phantom. Such is not the case if the deformity has been present only a few months before the extremity is removed. For example, a patient accidentally severed the flexor tendon of a ring finger which eventually resulted in a stiff finger. Seven years later the same hand was caught in a mangle, necessitating amputation just distal to the elbow. After this operation all the fingers of the phantom hand could be "moved" except the ring finger which was still stiff.

In no case in this series did the phantom limb that followed the amputation of an upper extremity of an adult disappear or even tend to fade

away. As stated, there were two subjects in whom phantom did not follow amputation. One, a 19-year-old girl, had lost an upper extremity at nine weeks of age. Another patient lost a right upper and right lower extremity in an accident at two and a half years of age. Now at twenty-nine years of age she too cannot recall ever having a phantom of either part. Another lost both upper extremities in a street car accident at three and a half years of age. In this instance both extremities had been amputated just below the shoulders. He is now forty-five years of age and as long as he can remember there has been a phantom on the left side but none on the right. So it may be said that amputation of an upper extremity before three or four years of age may be followed by a phantom part whereas the loss of an upper extremity during adolescence or adult life is almost invariably followed by the presence of a ghost hand that persists either continuously or intermittently throughout the remainder of the patient's life. In some, the ghost part is the site of intractable pain, interpreted by the patient as being due to cramps attending a distorted position of the part. This will receive further consideration later in this paper.

#### THE LOWER EXTREMITY

In contrast to the situation following the loss of an upper extremity, the phantom limb which appears after the removal of a lower extremity is less striking and is more likely to disappear spontaneously. There were 103 patients studied with loss of a major portion of one lower and 18 others with loss of both lower extremities. In addition one patient with amputation of an upper and lower extremity has been included in this group. These 122 patients had lost 140 extremities. Phantom limb followed the removal of 125 of these. The amputation had been performed through the thigh in 86 instances and below the knee in the remaining 54.

The following history illustrates the syndrome commonly present after a major amputation of a lower extremity.

I. M., a 22-year-old law student, developed gas gangrene of the left lower extremity following an operation on the knee joint. It became necessary to amputate at the level of the mid-thigh. There was no pain before the amputation was performed. He was brought to the operating room with the extremity lying in full extension and encased in a cast. This was the last recollection he had of the limb before the anesthetic was started. Upon regaining consciousness after the operation he perceived the presence of a phantom limb. The ghost consisted chiefly of a foot and the lower leg. It seemed bent so that when he was lying on his abdomen, the foot felt as though it was suspended above him. When he was lying on his back the foot seemed to be protruding through the mattress. The phantom foot was situated closer to the stump than normally. He felt that he could "move" the big toe of the phantom at will but not the other toes. The entire phantom was "asleep" and numb. The amputation stump healed promptly and he was subsequently fitted with a prosthesis. When the patient was examined five years after the amputation, he stated that the ghost foot had undergone no change except that it was not as vivid as it was when it first appeared.

The phantom part described by the patients in this group with major amputations of the lower extremities consisted mainly of a ghost foot. The big toe was especially prominent. In many patients the heel, the ankle and the lower part of the leg were represented and in a few the knee was also present. In three cases the entire missing limb was present in the phantom. As in the case of the upper extremity, the level of amputation in a lower member seemed to have little bearing on the size of the phantom. As a rule, the phantom seemed to be a replica of the original, however, in four the ghost foot was felt as being smaller.

Various sensations were described as arising in the phantom. Itching and tickling in the toes were mentioned by many patients while crawling, prickling or mild cramping were reported by others. Not uncommonly however, the phantom foot was described as feeling "natural."

In contrast to the abnormal position of the phantom of the upper extremity, the posture of the phantom of the lower extremity was not usually distorted. In most cases the foot seemed to be held at a right angle to the leg while the toes were described as being in the usual position of semi-flexion. In some instances the toes were reported as being cramped and pressed tightly together. A few patients stated that the toes were "bent under the foot". In cases where the toes of the ghost seemed tight or cramped, they felt as if they could not be "moved". In five instances the phantom member seemed to be hanging down under the bed as though it were protruding through a hole in the mattress. As previously noted, in the case of the upper extremity, deformities, especially those of long standing, that existed in the lower extremity before amputation, reappeared in the phantom limb. For example, in one patient, after a severe burn, the leg gradually became acutely flexed as a result of a cicatrix. The extremity was subsequently amputated at the level of the mid-thigh and the phantom which developed after amputation, was that of a flexed leg much the same as the posture assumed by the extremity before operation. There were numerous patients in the series who had lost one or several toes prior to undergoing amputation at a higher level. Only rarely were these losses perpetuated in the phantom.

In most cases the phantom lasted for one or two years. However, there were several exceptions to this. Thus, there were five subjects who still had a well marked phantom after 20 years, while another patient had experienced a phantom for 36 years and still another for 38 years. Usually the sensations associated with the phantom such as itching, tickling and so on, persisted for only a few months and disappeared long before the phantom.

#### MULTIPLE AMPUTATIONS

Amputations of the upper or the lower extremities bilaterally are usually followed by bilateral phantom parts, although the ghost hands or feet may not be identical. This is true, not only when the bilateral loss occurred as a

result of surgical procedures carried out at different times but also when the amputations were performed at the same time.

There were 22 patients in the series with major amputations of two extremities. In 18, major portions of both lower extremities had been removed, while in three others major parts of both upper extremities had been amputated. In the remaining patient a single upper and lower extremity on the same side had been removed. In one patient both lower extremities had been accidentally severed at the same level just distal to the knee. Although the level of surgical amputation was nearly identical on both sides, the phantom foot was much more in evidence on the left. Furthermore, the toes of the phantom on the left were said to be itchy while those on the right were not. Often the ghost image was more enduring on one side than the other. Also a greater portion of the missing limb was usually represented on one side.

#### AMPUTATION DURING CHILDHOOD AND ADOLESCENCE

*Children.* Children may have a phantom limb after the amputation of an extremity. There were 16 patients in the group who were 12 years old or less at the time of amputation. A total of 18 major amputations had occurred in this group and a phantom limb followed amputation in eight cases. The majority of these individuals were adults at the time of this study. As previously stated, the youngest subject with a phantom had lost the upper extremity at three and a half years of age. The youngest patient with a phantom limb following the removal of a lower extremity was four years old at the time of amputation. The phantoms that followed amputations during childhood and that persist into adult life are described as the same regardless of the age at the time of amputation.

*Adolescents.* There were 12 subjects in this group who had sustained a major amputation while between the ages of 13 and 16 years. A total of 15 major losses had occurred in the adolescent group. All of these patients developed typical phantom limbs. A single upper extremity had been removed in four patients while a single lower extremity had been removed in five others. Two of the remaining patients had sustained a loss of both upper extremities and one other individual had sustained the loss of both lower extremities.

#### MISCELLANEOUS FACTORS RELATED TO THE AMPUTATION AND THEIR BEARING ON PHANTOM LIMB

It is recognized that the extremities on the dominant side of the body receive preferential use all through life. One might expect then that the removal of an extremity, especially a hand, from the dominant side would result in a more lasting and perhaps a more striking phantom part. This has not been found to be true. The best opportunity to evaluate a phantom part in its relation to limb dominance occurred in those patients who had sustained simultaneous bilateral amputations of upper extremities. There were 11 such individuals in the group. Some of these patients stated that both

phantoms were equally striking, while others could not be sure which was the more prominent. In some instances the phantom on the dominant side was not as well perceived as that on the opposite side. Comparing the lengths of time each ghost endured it was found that the hallucination on the dominant side did not last significantly longer than the one on the other side. Furthermore an analysis of patients with amputations of single extremities showed that limb dominance had very little effect either on the character or the duration of the phantom.

Some observers have stated that amputation through the forearm or leg is more likely to give rise to a lasting phantom limb than an amputation performed more proximal. A comparison of the duration of the phantoms resulting from 64 low-level removals (below the elbow or knee) and 95 high-level removals did not support this statement.

It was found that if an extremity was accidentally severed the resulting phantom was more likely to be enduring. As already noted, the phantom which followed the removal of an upper extremity is likely to last for a longer period than the one which appears after the loss of a lower extremity. Most of the amputations of the upper extremity in this series occurred as a result of accident.

Wound healing, either primary or secondary, seems to have little effect on the occurrence, type or duration of phantom limb. There were 32 amputations in the series where delayed healing of the amputation stump had occurred and 127 other stumps in which primary healing of the operative site had taken place. Furthermore, it was found that poorly constructed stumps did not produce any significant alterations in the phantom limb. Protruding ends of bone, unnecessarily large flaps of tissue or tight flaps were present in some and were often the cause of local pain in the stump. While these features frequently prevented the patient from wearing a prosthesis they apparently had no influence on the phantom part.

#### PAINFUL PHANTOM LIMB

In the entire series of 159 surgical amputations in 137 patients there were 48 painful phantoms in 47 of these, 38 male and 9 female. A critical review discloses that the level of amputation, the nature of the wound healing, whether the extremity was amputated for a disease process or as a result of trauma, whether the extremity was the dominant one or not or whether the stump tissues were redundant or taut seemed to have little if any bearing on the two types of discomfort that are subsequently described as transitory and enduring painful phantom. Pain in the extremity prior to amputation seemingly influences the presence of pain in the phantom limb. This was true for both transitory and enduring pain. Of the 38 cases with transitory pain, 26 had severe pain before the extremity was removed. Of the ten examples with enduring pain in the phantom six had severe pain before amputation.

Considering every case where an amputation was followed by a phantom limb, the incidence of painful phantom limb was approximately 30 per cent. The syndrome of painful phantom limb is frequently confused with painful neuroma or causalgia of the stump. Pain arising from neuromas is distinctly local in character. The discomfort in such cases is intermittent and occurs when the end of the stump is mechanically stimulated. The distress is sharp and often electric-like. The pain arising from stimulation of neuromas is frequently referred out to the phantom limb, if present, but does not originate in the ghost part itself. Jumping stump may be associated with the attacks of pain. The discomfort may be promptly abolished by injections of procaine into the painful neuroma. Causalgia of a stump is more apt to occur after amputation of a digit than after the removal of a major portion of an extremity. In a few cases the stump was the site of severe burning pain. In stump causalgia, a light touch often initiates burning pain that may involve the whole stump. These patients will not permit the part to be handled and at times they are unable to bear even the weight of clothing on the stump. Exposure to a cold draught is often sufficient stimulus to initiate pain. On examination the stump in such cases is found to be cold, sweaty, cyanotic and somewhat atrophic.

In reviewing the complaints of the patients in this group with pain in the phantom limb, exclusive of the causalgias and neuromas, it became evident that they fell into two divisions. In the first division the discomfort was transitory and showed a progressive tendency to diminish in severity as time went on. In the second, the pain was enduring and showed no tendency to relent as time passed. In those with transitory pain in the phantom the discomfort was characterized by the presence of bothersome dysesthesias such as numbness, tingling or burning, whereas in those with enduring pain the distress was characterized by an unalterable postural distortion of the phantom member.

#### TRANSITORY PAIN IN THE PHANTOM LIMB

In 38 instances bothersome distress of a transitory nature was present in the phantom part. In two cases transitory pain in the phantom was associated with loss of an upper extremity while in 36 others the lower extremity was involved.

As stated the discomfort in those considered to have transitory pain was usually described as a sensation of bothersome burning, tingling, coldness, numbness, fullness or occasionally electric shocks in the ghost member. In most instances the pain appeared on the day after operation or shortly thereafter. However, in one instance the pain came 13 years after amputation, in another three years and in another four months after operation. Commonly the discomfort was fairly severe for several weeks after operation followed by a gradual subsidence. In 27 cases the pain had disappeared after 12 months. In seven others, it had totally subsided after 24 months. In the remaining four the distress had persisted for three, five, seven and

ten years respectively, but in each of these the pain was considered to be gradually disappearing. In 12 of the 38 cases the pain in the phantom bore a distinct resemblance to the discomfort present in the extremity before amputation. Among this group of patients with transitory pain in the phantom limb, there were four with bilateral losses of the lower extremities. One patient experienced distress of a temporary character in both phantoms. Two had bilateral phantom limbs but in each instance pain was present in only one side. The remaining patient had a phantom limb on only one side associated with mild pain in this ghost part.

#### ENDURING PAIN IN THE PHANTOM LIMB

In ten instances, the phantom limb was the seat of enduring and unrelenting pain. In four cases the pain in the ghost member had followed the removal of an upper extremity, while in the other six it developed after the loss of a lower extremity. The following case history is illustrative of this syndrome in the upper extremity.

J. B., a 53-year-old white male, sustained an avulsion injury of the right upper extremity in an auto accident. A few hours later amputation was carried out through the upper arm. He could not recall having any pain in the member prior to its removal. Immediately after awakening from the anesthetic there was a phantom limb. The ghost part was lying in front of his chest and seemed to be situated close to the amputation stump. The lower arm, elbow and forearm were not represented. The fingers of the phantom were held in extension with the tips pressed together. A sensation of cramping was present in the ghost and the fingers felt uncomfortable. Gradually the phantom hand became more distressful so that by the third month after operation the pain was continuous. A pressing and squeezing sensation was now present involving the palm and all the fingers. The fingers were so tightly pressed together that it seemed as though they were being crushed in a vise. The wrist was also painful and felt as though a wire noose had been tightened about it. He discovered that the pain became worse when the weather was inclement. If the end of the stump was accidentally struck, a shock-like sensation radiated out to the ghost part, however, under these conditions the squeezing pain remained unaltered.

The syndrome of intractable pain as related to amputation of the lower extremity is illustrated by this case:

I. S., a 60-year-old white male with obvious arteriosclerosis, developed gangrene of the right foot. The gangrenous toes had become gradually insensitive and they were finally removed without the use of an anesthetic. Shortly afterward a cellulitis of the foot developed associated with severe pain in the entire involved limb. Seven weeks after this the extremity was amputated through the mid-thigh. After recovering consciousness there was a phantom limb. The lower leg and the foot were represented in the phantom. At first the phantom limb was not painful; however, two weeks after operation there was a severe cramping sensation in the ghost foot. Over a period of several weeks this distress gradually became more severe and the phantom felt as though it were being forcibly bent on itself. After great effort the foot could be "straightened" slightly and the pain would temporarily lessen. Narcotics were resorted to and had been continued up to the time of examination.



In every instance where the phantom was the seat of intractable pain the outstanding clinical feature was painful postural distortion of the ghost. As a result of this the patient complained of unrelenting cramping, squeezing or twisting of the phantom part. In a few instances temporary respite from pain followed "voluntary movement" of the ghost. In no case did the distress show any tendency to abate with the passing of time. After the removal of an upper extremity one patient stated that the nails and fingers felt as though they were being dug into the palm of the ghost hand. Another patient stated that his phantom hand was perpetually clenched in a tight fist so that he could not open it. Following amputation of a lower extremity another complained of having the feeling that the toes were being bent into the sole of the phantom foot. Another described his ghost foot as having a tight wire twisted around it and the toes felt as though they were being squeezed. Still another individual stated that his ghost foot felt as though it were encased in a block of cement and that the foot could not be moved.

In each of the ten cases, the distortion of posture involved the distal portions of the phantom. Patients with pain due to such unalterable abnormal posture of the phantom are the ones that may be relieved by dorsal cordotomy.

#### DISCUSSION

Following the loss of a part of the body, either by operation or accidental trauma in the adult human, there is a perpetuation of the patient's body image. It rarely occurs if the part, especially an extremity, has been removed during early childhood and in our experience has not been present in those in whom the part was removed before the third year of life. It is never present in subjects born without extremities. We find nothing so remarkable about this. In truth, the adult subject who refuses to admit the presence of a phantom limb after the amputation of a major part of it, is to be considered psychologically abnormal. Long-standing deformities of, as well as absence of, digits of a hand or foot that have been established in any particular individual's body pattern should be expected to be perpetuated in the phantom if the extremity of which the abnormality was a part were removed later in life. This too we have found to be the case. This perpetuation of the body pattern that has been called ghost or phantom part, is not what has attracted our attention but the fact that in many instances the phantom is not a replica of the part removed. Especially has our attention been attracted to those patients with pain that is described as residing in a miniature ghost of the part removed and at times resulting from an unalterable cramped posture of the fingers or toes of the phantom hand or foot.

Several theoretical explanations have been proposed for this most remarkable phenomenon, notably that impulses arising from the stumps of the severed nerves upon reaching the cerebral cortex are interpreted as coming from an extremity that is smaller and often distorted. Such a concept seems

untenable. There were ten patients in the present series with phantom limb who were subjected to reamputation of the stump. Sectioning the nerves of the stump at a higher level produced no changes in the phantom. It seems most unlikely that the surgeon could have sectioned the nerve trunks at the second operation precisely as they were divided at the first operation. Moreover, experience has shown that sectioning all the spinal nerves introdurally that supply the stump of an extremity has no bearing on the size or posture of a phantom, nor does such a procedure relieve or change the character of pain that seems to reside in the phantom. One patient in the series sustained a traumatic amputation of the forearm associated with an avulsion of brachial plexus of the same side. The remaining stump of the arm was totally devoid of all sensation yet there was a phantom hand that was described as being in a continuous painfully cramped posture.

Anterolateral cordotomy with resultant loss of pain and temperature of the stump has produced transitory alterations of the phantom in a few, whereas in others there was no change in the size and posture of the phantom nor the character of the pain. This operation has relieved the pain associated with overgrowth of nerve stumps, the so-called painful stump neuromas. It has had very little if any beneficial effect on the burning pain of causalgia. Leriche<sup>2</sup> and Livingston<sup>3</sup> have emphasized the role of the sympathetic nervous system in connection with painful phantom limb. Sympathetic denervation of a stump may favorably influence a painful phantom part for several weeks; however, from our experience, lasting benefit should not be expected to follow sympathetic ganglionectomy.

In 1911, Head<sup>4</sup> reported the disappearance of a phantom limb following thrombotic infraction of the sensory cortex contralateral to the ghost part. Guiterrez-Mahoney<sup>5</sup> has shown that selective excision of a part of the parietal cortex may modify phantom limb and produce transitory reduction in the pain residing in the ghost. We have indicated in a previous report that the cramp-like pain in a phantom hand or foot that has been described by the patient as the result of an unalterable posture in the ghost may be favorably altered by surgical section of the fibers of the dorsal spinal cord on the side of the disturbance. Both of these procedures (parietal cortical ablation and dorsal cordotomy) are designed to deprive the patient of a knowledge of the stump as well as the phantom. Certainly one would not expect that either the cerebral cortical ablation or section of the fibers in the spinal cord that allegedly carry proprioceptive sensibilities would favorably influence pain produced by a neuroma or the other clinical syndromes characterized by pain that may arise from scarring in the end of the stump. It must therefore be clearly recognized that the selection of the patients to be subjected to either of these operative procedures must be made with great care. Approximately 100 per cent of adult patients who lose an extremity will have a phantom limb lasting for variable periods after operation. About one-third of these will suffer from pain in the stump

and/or the phantom and in 75 per cent of these the pain will slowly disappear. A small percentage (approximately 7 per cent of the total number) will have a more or less continuous cramp-like pain in the phantom hand or foot due to abnormal posture of the ghost. It has been our experience to date that complaints of this character coming within a week or so following operation are likely to continue throughout the remainder of the patient's life unless modified by a surgical procedure designed to deprive the patient of a knowledge of the position of the ghost part.

#### TREATMENT AND RESULTS

Our surgical experience has been limited to dorsal cordotomy. As stated, selection of the patient for operation is of utmost importance. Only those with pain in the phantom due to cramped abnormal posture of the ghost should be subjected to this operation. Six patients have been operated upon, two with painful phantom hands and four with distorted painful phantoms of the legs and feet. The cordotomy for the abnormalities of the upper extremity should be performed at the level of the second cervical spinal segment. The lateral two-thirds of the dorsal column of the cord may be sectioned without disturbing gait or station. For the lower extremity the tractotomy should be performed at the mid-thoracic level and all of the fibers of the dorsal column on the side of the phantom are to be sectioned. With the spinal cord exposed and the arachnoid removed, the dorsal sulci may be identified by dropping some blood on the cord and observing the red blood cells collect in these grooves. An alternate method is to make the sulci prominent by applying a small amount of neutral methylene blue to the surface of the cord. Following dorsal cordotomy there is no demonstrable disturbance in rectal or vesicular sphincters nor motor power of the stump. Appreciation of touch was not altered. In three patients there was impaired but not marked loss of appreciation of vibration of the tuning fork below the level of the section of the spinal cord. Appreciation of passive motion of the stump was impaired in three, however, this mild disturbance disappeared within about three months following operation. Complete loss of the phantom foot and the cramp-like pain resulted in three. In the remaining patient with phantom foot the pain was relieved but "at times the phantom is still there". Hypnotics were no longer used and there was a gain in weight. The results in the two patients with phantom upper extremities were not so good. At least the results are difficult to evaluate. One of these (a World War II veteran) before operation complained of cramp-like pain in a small phantom hand that seemed to be "close to but not connected with" a short stump of the left arm. In addition there was a burning sensation in the phantom that was said to be in the region of the hypothenar eminence. After operation performed by Dr. Frank Turney, the phantom hand was still present and there was "some burning" in the hypothenar region of the ghost. He flatly denied ever complaining of a cramp-like pain

in the phantom, the outstanding distress before operation as recorded by three competent observers. The other patient with painful distorted phantom of the left upper extremity was a none-too-intelligent negro approximately sixty years of age. Before operation there was a complaint of continuous cramp in the ghost hand. He was frequently seen to be holding the stump of the left arm with the right hand. After operation the phantom part was not mentioned by him unless inquired into by the house staff. If asked directly regarding the ghost part it seemed that there was intermittent burning type of pain in the stump of the arm and that the phantom was present if attention was focused on it.

From the results obtained from dorsal cordotomy up to the present time we believe the procedure has merit and its use should be continued. Certainly the results in the patients with phantom foot are most encouraging.

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DISCUSSION.—DR. GILBERT HORRAX, Boston: I think one of the curious things in phantom limb pain is this cramp-like pain in the extremity. Most patients complain that the hand is in an extremely cramp-like position and they cannot get it down. The causalgia-like pain that some of them have, if it is helped by anything, is helped by sympathectomy. Dr. James E. White brought that out, I think, in a discussion of war cases. This cramp-like pain is not helped by sympathectomy, at least in our experience. Cordotomy, in our experience, is useless with these amputation pains. Other procedures have been used, and Dr. Mahoney some years ago did several cortical incisions of the sensory area for the painful phantom. I understand that he has said recently that the pain in those patients returned. I carried out cortical incision in one patient who had bilateral amputation of the upper extremities, doing it on both sides. He was relieved only for a week or two, then the pain recurred and was as bad as ever. I think I was ill-advised to do this so far as that particular patient was concerned, because although we got him off morphine he had become an addict and went back to it eventually. It is my feeling that in a case of that type, probably a lobotomy might succeed, although that remains to be seen. But cortical excisions for this type of pain have not been successful in my hands. Therefore I think that if dorsal cordotomy, which is a relatively simple operation, will eliminate this severe cramp-like pain, Dr. Browder has made a distinct contribution to neurologic surgery.

# A COMPARATIVE STUDY OF SUBTOTAL GASTRECTOMY WITH AND WITHOUT VAGOTOMY\*†

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THERE SEEMS TO BE LITTLE DOUBT that severance of the vagus nerves to the stomach produces physiologic changes which promote peptic ulcer healing and possibly prevent recurrences in the majority of cases. However, some surgeons have abandoned vagal section as the sole procedure in the surgical therapy of chronic non-obstructive duodenal ulcer because there have been recurrences despite complete vagotomy as verified by negative insulin tests, and because the high incidence of persistent gastric atony frequently required further surgery for correction. The addition of a gastro-enterostomy to bilateral infradiaphragmatic vagotomy usually eliminates the symptoms of gastric motor disturbances. It has long been recognized that gastro-enterostomy per se will heal a duodenal ulcer, but the fact that this operation is followed by a high incidence of jejunal ulceration has minimized its usefulness. Whether the addition of vagus section will prevent this untoward complication will be decided only by future follow-up observations. We, as well as others, are employing this combined procedure in a series of selected cases, and while the results to date appear promising, insufficient time has elapsed to warrant definite conclusions.

Although subtotal gastrectomy of the Billroth II type is still the procedure of choice for duodenal ulcer in many clinics, it has not met with universal approbation. Its critics have stated that in the hands of the average surgeon the mortality is too high and that the end results do not justify the magnitude of the procedure. However, the mortality and morbidity in experienced hands has been markedly reduced in recent years. It is true that following gastric resection some patients fail to gain weight, some are rendered uncomfortable by the dumping syndrome, and a certain number develop jejunal ulceration. The incidence of this latter complication has been reported as between 3 and 9 per cent. Most of these occur in the presence of high free acid values in the gastric contents. If subtotal gastrectomy, which removes the hormonal phase of gastric secretory activity, is combined with bilateral infradiaphragmatic vagotomy, which eliminates the psychic phase of gastric secretion, it is reasonable to predict a further lowering of the acidity or the production of an achlorhydria. Under these conditions, the incidence of jejunal ulcer should be reduced, for it is well known that jejunal ulceration does not occur in the absence of free hydrochloric acid.

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The combination of subtotal gastrectomy and infradiaphragmatic vagotomy for duodenal ulcer is not a new concept. In 1929, Klein<sup>1</sup> published the results of left anterior vagotomy and gastric resection in eight cases of duodenal ulcer with unusually high preoperative acid figures. All cases revealed an achlorhydria to the gruel Relfuss test within six months after operation. In a control series treated by gastrectomy alone, only 25 per cent developed an achlorhydria. Subsequently in 1934, Winkelstein and Berg<sup>2</sup> reported further studies in 34 cases of duodenal ulcer with high preoperative acidity in which twenty-six, or 77 per cent, developed achlorhydria to gruel following partial gastrectomy and left subphrenic vagotomy.

It was therefore considered logical to combine subtotal gastrectomy with infradiaphragmatic bilateral vagotomy provided the operative risk and postoperative morbidity were not appreciably increased. At first, this combined procedure seemed especially indicated in the duodenal ulcer cases in which bleeding without pain was the predominant symptom, and those in which the preoperative acid studies were unusually high, two categories in which subsequent jejunal erosion and ulcer are most apt to occur. Accordingly, early in 1946, subtotal gastrectomy and complementary bilateral infradiaphragmatic vagotomy were performed on several of these patients without mortality or significant additional postoperative morbidity. Encouraged by the immediate results, the indications were broadened and the combined procedure was performed with increasing frequency. Other similar cases in which subtotal gastrectomy alone was done for duodenal ulcer were used for comparison. It might prove informative to review these two series to determine the advantages and disadvantages of the combined procedure.

This presentation must be considered as a preliminary report for the ultimate results of any ulcer therapy must be based on follow-up studies extending over a period of many years.

The cases studied represent all the duodenal ulcers admitted during the years 1946 and 1947 to the C Ward Service of the Mount Sinai Hospital and to the private service of the senior author, in which subtotal gastrectomy with and without vagotomy were done. All of these cases had had previous medical treatment. The average duration of symptoms was more than 12 years, and the average age of the patients was 45 years. There were 100 such cases, 12 of which had been operated upon previously for acute perforations. Fifty-four patients were treated by subtotal gastrectomy and 46 by subtotal gastrectomy combined with bilateral infradiaphragmatic vagotomy.

The incidence of untoward reactions at the time of operation was minimal in both groups. One case in the gastrectomy series suffered a sudden sharp drop in blood pressure and a rise in pulse rate toward the end of the procedure. A similar change was noted in one patient when the vagus nerves were mobilized and resected. In view of the fact, however, that in this clinic the infradiaphragmatic vagotomy is performed after the gastric resection, these circulatory effects cannot be ascribed to the vagotomy. No other sequelae

such as bradycardia, vagovagal reflex or cardiac arrest were noted. However, in one case, while attempting to mobilize the esophagus, it was partially torn longitudinally. The laceration was sutured, but the vagus nerves were not sectioned. The patient made an uneventful recovery.

There were no deaths in either group in this series.

A comparison of the early postoperative complications revealed some differences between the two series. The postoperative course was rated as minimal, moderate or severe. In the gastrectomy group of 54 patients, 48 were classified as minimal, five as moderate, and one as severe. In the gastrectomy-vagotomy group of 46 cases, 31 were classified as minimal, 13 as moderate, and two as severe.

A summary of the complications in the two series are listed in Table I.

There were six cases with pulmonary complications in the gastrectomy group, all of which were mild; there were ten in the gastrectomy-vagotomy group, eight mild and two severe.

Five cases in the gastrectomy group developed postoperative retention and vomiting, which in two were rather distressing and prolonged. Six patients of the gastrectomy-vagotomy group suffered from similar symptoms but these were severe in only one.

TABLE I

	Subtotal Gastrectomy	Subtotal Gastrectomy and Infradia- phragmatic Vagotomy
Pulmonary .....	6	10
Vomiting and retention .....	5	6
Diarrhea .....	4	5
Distention .....	1	3
Dysphagia .....	0	4
Duodenal fistula .....	1	4
Pelvic exudate .....	0	2
Subhepatic exudate .....	0	2
Evisceration with intestinal obstruction.....	0	1

A mild diarrhea occurred in four patients of the gastrectomy series. However, one of these was obviously due to the effects of jejunal alimentation and subsided promptly when these feedings were discontinued. The gastrectomy-vagotomy series contained five cases with diarrhea. In the only one which was severe, stool cultures revealed that the patient was suffering from a *Salmonella* infection. Another patient had a penicillin reaction, which produced a rash, fever, and diarrhea. It was felt that for purposes of comparison, these two cases might be discarded. A corrected incidence of diarrhea disclosed three mild cases in the gastrectomy series, and three mild cases in the gastrectomy-vagotomy series.

Marked abdominal distention was noted in only one case of the gastrectomy group, and that occurred in the patient previously mentioned, who had had a complementary jejunostomy. In the gastrectomy-vagotomy series there were three cases with moderate postoperative distention due to peritonitis rather than vagotomy. All of these were observed in patients in whom the duodenal closure had been difficult, and the area had been drained. A temporary duo-

denal fistula developed, and in two of these cases, subhepatic and pelvic exudates resulted, which subsided spontaneously.

Four patients in the gastrectomy-vagotomy group complained of substernal pressure and pain on swallowing which occurred in general about the second postoperative week and lasted for about ten days. It was assumed that this was caused by the reaction to mobilization of the mediastinal esophagus.

Gastric secretion studies before and after subtotal gastrectomy for duodenal ulcer have been previously reported by Winkelstein<sup>3, 4</sup> of this clinic. (Table II.) Postoperative secretion studies in the present gastrectomy series were not routinely performed.

Preoperative gastric secretion studies in the gastrectomy-vagotomy group revealed the usual hyperchlorhydria found in duodenal ulcer patients. The postoperative secretion studies in 39 of the 45 patients in the gastrectomy-vagotomy group are summarized in Table III.

TABLE II.—*Postoperative Secretion Studies After Subtotal Gastrectomy (Winkelstein)*

Test	No. of Cases	Anacid	Free acid Present	Percent Achlorhydria
Gruel .....	85	47	38	55
Night .....	21	14	7	67
Histamine .....	31	13	18	42

TABLE III.—*Postoperative Secretion Studies (Gastrectomy-Vagotomy Group)*

Test	No. of Cases	Anacid	Free Acid Present	Percent Achlorhydria
Gruel .....	12	12	0	100
Night .....	20	19	1	95
Histamine .....	28	21	7	75
Insulin .....	24	20 (or negative)	4 (positive)	83

TABLE IV.—*Symptomatology 4 to 28 months postoperatively*

	Subtotal Gastrectomy (46 cases)	Gastrectomy-Vagotomy (40 cases)
Pain .....	3	2
Blceding .....	1	0
Vomiting .....	5	2
Diarrhea .....	1	5
Dumping .....	0	1

A comparison of the results of the secretion studies following subtotal gastrectomy reported by Winkelstein with those of the present gastrectomy-vagotomy group reveals a decided increase in the percentage of postoperative achlorhydria.

Despite the small number of patients tested by the gruel Rehfuß, the difference between the percentage of achlorhydrias (Table II and III) is large enough to be considered significant. The gruel test stimulates both the psychic and chemical phases of gastric secretion. After subtotal gastrectomy alone, 55 per cent of the cases were anacid to gruel. The addition of vagotomy produced an achlorhydria in all 12 patients examined. The number of patients



tested by the gruel Rehfuß was small, inasmuch as this test was not done upon patients anacid to histamine.

The night secretion studies in the gastrectomy-vagotomy group revealed achlorhydria in 19 of the 20 patients tested, as compared to 14 of 21 following subtotal gastrectomy. It is significant that the one patient in whom free acid was present in the night secretion gave a hospital insulin test indicating incomplete vagotomy. Postoperative night secretion studies in both these groups reveal an essential difference from those in which vagotomy was employed as a sole procedure. In the latter, the night secretion was definitely diminished both as to volume and acid concentration, but achlorhydria was rarely obtained.

It is difficult to explain the increased incidence of histamine achlorhydria following the combined procedure when compared to gastrectomy alone, since histamine stimulates directly the acid secreting cells. This problem awaits further investigation. The interpretation of the insulin response will be the subject of a future communication.

Although these acid secretion studies are based on a small number of cases, they indicate that the addition of bilateral infradiaphragmatic vagotomy to subtotal gastrectomy produces a higher percentage of achlorhydrias than has

TABLE V.—*Early Follow-Up Results—4 months to 28 months*

	—Gastrectomy—		Gastrectomy- —Vagotomy—	
	No. of Cases	%	No. of Cases	%
Well .....	38	83%	34	85%
Improved .....	7	15%	6	15%
Unimproved (jejunal ulcer).....	1	2%	0	0%
	<hr/> 46	<hr/> 100%	<hr/> 40	<hr/> 100%

been attained by any other medical or surgical therapy. It must be remembered, however, that many of these test meals were performed soon after operation and it is possible that there may be significant changes in subsequent studies.

In the evaluation of follow-up results, it is important not only to establish the presence or absence of jejunal ulceration, but also to determine whether there are any distressing symptoms attributable to altered gastric function. Eighty-six patients were personally interviewed four to 28 months after operation. They were specifically questioned about pain, bleeding, vomiting, diarrhea and evidences of the dumping syndrome. In the few cases in which these symptoms were present, they were usually mild.

Most patients in both groups experienced some post prandial fulness or distress for a short period after operation. However, this was mild and transient. Two patients in each group complained of pain characterized by fulness, epigastric oppression, and occasionally cramps. In addition, one had typical ulcer pain, which was accompanied by bleeding 11 months after subtotal gastrectomy without vagotomy. He was treated conservatively for a jejunal ulcer, and for the past few months has been well.

Comparison discloses that occasional vomiting was more frequent in the gastrectomy group and a mild diarrhea more common in the gastrectomy-vagotomy group. An interesting finding in the latter group was the frequent relief of habitual constipation.

The dumping syndrome was seen in only one patient in this series. This occurred after subtotal gastrectomy with vagotomy. The symptoms, however, have become progressively milder during the past year.

On the basis of follow-up observations, these patients were classified as well, improved or unimproved. (Table V.) In the gastrectomy group, in which 46 patients were followed, 38 were well, seven were considered improved but not entirely well because of the presence of one or more of the symptoms previously described. The one patient who developed a jejunal ulcer was considered unimproved.

In the gastrectomy-vagotomy group, 40 cases were followed; 34 were well and six were improved.

#### DISCUSSION

The addition of infradiaphragmatic vagotomy to subtotal gastrectomy in this group of patients has not caused any mortality but has added to the immediate postoperative morbidity. The reaction to operation was somewhat more severe, and the pulmonary complications were more frequent. While gastric atony is a common complication after vagotomy alone, its effects are minimal when subtotal gastrectomy is performed simultaneously. Gastric retention and postoperative vomiting were infrequent and mild in both groups. Severe diarrhea was not seen in this series, and a mild diarrhea occurred with the same frequency in the two groups during the early postoperative period. Subsequently loose bowel movements were more common in the gastrectomy-vagotomy group.

Abdominal distention was not seen frequently in either series, and could not in any case be attributable to the vagotomy. The substernal pain following infradiaphragmatic vagotomy occurred in four of the 46 cases and was never very disabling or prolonged.

Acid secretion studies indicate that the combined procedure favors the production of an achlorhydria, the presence of which, in our experience, precludes the development of recurrent ulcers.

Follow-up studies have revealed that the differences in symptomatology in the two groups were not significant. One jejunal ulcer was diagnosed clinically in the gastrectomy series, but it is too early to draw conclusions regarding the ultimate recurrence rate in either group.

#### SUMMARY

1. Theoretically, subtotal gastrectomy with bilateral infradiaphragmatic vagotomy should diminish the incidence of jejunal ulcer.
2. The addition of vagotomy to subtotal gastrectomy in this series did not cause any mortality.

3. The combined operation resulted in an increase in the immediate post-operative morbidity.

4. The disabling symptoms of gastric atony commonly seen after vagotomy alone were not present when the combined operation was used.

5. There is a higher percentage of achlorhydrias following the combined procedures than with subtotal gastrectomy.

6. Future follow-up observations in these groups will determine whether subtotal gastrectomy combined with bilateral infradiaphragmatic vagotomy will lower the incidence of jejunal ulcer.

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DISCUSSION.—DR. LESTER R. DRAGSTEDT, Chicago: I am somewhat surprised that Dr. Colp and his associates have apparently been unable to secure satisfactory results in the treatment of peptic ulcer by vagotomy alone or by vagotomy combined with gastroenterostomy, in those cases that have obstruction at the pylorus. In our clinic this operation has made its way until at the present time all the surgeons in our hospital prefer the operation of vagotomy alone or vagotomy plus gastroenterostomy to subtotal resection.

Up to this time a total of 430 of these operations have been performed and we are all agreed that the results are more satisfactory than we have seen from subtotal gastrectomy. It would seem to me that a combination of the two procedures is unwarranted at the present time. I feel certain that a large number of patients will lose an important digestive organ unnecessarily. The great majority of these patients can be cured, and will stay cured for a long period of time, if vagotomy alone is done. It is true that postoperative management is a little more difficult with vagotomy alone than if the operation is combined with gastroenterostomy. That is due to the necessity for controlling the postoperative decrease in tonus and motility of the stomach. In our clinic, however, we are successful in doing this, and at the present time we have no difficulty on this score.

I should like to recommend that greater attention be paid to postoperative management when vagotomy is done, and to remind you that the results now secured in the treatment of peptic ulcer by subtotal gastrectomy are much better than when this operation was first introduced, before surgeons had become well acquainted with the technic of the procedure and the technic of postoperative management.

DR. OWEN H. WANGENSTEEN, Minneapolis: I should like to speak of a new indication for gastric resection for ulcer disease. Before doing so, however, I wish to comment briefly on one item in this discussion, viz., the value of vagotomy as an auxiliary procedure in an operation which of itself is not adequate to thwart the threat of recurrent ulcer. Accumulating evidence suggests that a vagotomy must be complete, as Dr. Dragstedt has suggested, or there will be no effect from the vagotomy. Moreover, a complete vagotomy, even in experienced and practiced hands, appears to be difficult to achieve consistently. Vagotomy does provide definite protection against

ulcer both in patients and against the histamine provoked ulcer in the dog. Dr. Dragstedt ascribes this protection to reduction of gastric acidity; my associates and I are inclined to believe from our studies concerning the nature of the protection obtained by vagotomy against the histamine provoked ulcer in dogs, that it is owing largely to delay in gastric emptying. In other words, converting the human or the dog's stomach into a rabbit-type of stomach, in which food is always present, in itself affords considerable protection against ulcer. When, however, gastrojejunostomy or a small gastric resection is added (25 to 33 per cent), the protective action of the vagotomy against the histamine provoked ulcer seems to disappear. It is unfortunate that we do not have a critical objective test against which the protective action of vagotomy can be assessed. The resolution of the efficacy of an operation by clinical trial is not a promising prospect; witness how long it took us to decide that gastrojejunostomy was an unsatisfactory operation for ulcer.

In the first Book of Samuel, we read of Saul, who went in search of his father's asses and found himself a king. Now there are those who profess to go in quest of a king and find asses instead. In "The Three Princes of Serendip" Horace Walpole invents the designation serendipity to indicate finding something not sought after. Such is the nature of the windfall which befell me when I undertook on the first Sunday in September, 1939, to do an emergency gastric resection for a patient with massive hemorrhage from a bleeding duodenal ulcer. The patient had been dilated more than 100 times for a coincidental esophageal stricture by Dr. N. Logan Leven of our Department of Surgery. We had expected fully to have to continue dilating the patient's esophagus interminably, but much to our amazement, it soon became apparent that no further dilatations were necessary. In the intervening nine years, gastric resection has now been done in six such cases with startling results. One of these is a recent patient who carried a gastrostomy for eight years because he could not swallow his saliva. He too had a coincidental duodenal ulcer. A year has intervened now since gastric resection was done in a boy aged 17, for a stricture of unknown origin beginning in the mid-esophagus. He has remained well and swallows solid food of every kind. Prior to operation he could swallow only liquids. In another patient with a congenitally short esophagus and a corkscrew like stricture of the lower esophagus, four years have elapsed since gastric resection was undertaken. She too had submitted to approximately 100 dilatations of the esophagus prior to operation. Two dilatations were done during the early months of convalescence and more have been necessary since.

These patients usually have a good deal of free HCl in their gastric secretion. Moreover, Dr. Leven and I are inclined to believe, in consequence of this experience, that esophagitis or esophageal stricture is essentially a manifestation of ulcer disease. Moreover, the squamous epithelium of the esophagus is more susceptible to injury by the acid-peptic digestive juice than is the gastric mucosa. Duodenal ulcer is the most frequent variety of ulcer—only because the duodenum is the sole exit for the gastric contents. If the esophagus were the exit for the stomach, rather than the duodenum, every person probably would have esophagitis or acid-peptic ulcer of the esophagus because of the low threshold of resistance of the esophagus to digestion by the gastric juice. Both in the rat and in the pig, in which animals there is a ring of squamous epithelium in the stomach about the esophageal aperture, when histamine is given, ulcers occur regularly in the proventriculus (area having esophageal epithelium) and not in the glandular portion of the stomach.

An undisciplined imagination may be as dangerous as a roving eye. Nevertheless, it is difficult to escape the impression that cardiospasm and esophageal strictures too may be kept active by the regurgitation of the irritating acid-peptic digestive juice. In any case, I feel justified in exploring the possibility. So far one patient with cardiospasm of long standing has been subjected to gastric resection and with considerable im-

provement. In any case, I feel justified in suggesting that esophagitis and esophageal stricture may be manifestations of ulcer disease and may be relieved by an effective gastric resection.

DR. RALPH COLP, New York (closing): I want to thank Dr. Dragstedt and Dr. Wangenstein for their discussion. Subtotal gastrectomy as the procedure of choice has been used in our clinic for about twenty-five years. We are satisfied with the procedure. What worries us is the incidence of recurrent jejunal ulceration. As you know, we have the class of patient who has been subject to stress and strain, and therefore if we could eliminate the psychic phase of gastric secretion by infradiaphragmatic vagotomy, we thought perhaps we might diminish the incidence of jejunal ulceration by combining it with subtotal gastrectomy. We are rather reluctant to give up this procedure, although we know there are innumerable clinics now which are performing vagotomy as a solitary procedure, or combined with gastroenterostomy. As a matter of fact, I think this question will be solved within a reasonable time, because at the last review made by the American Gastroenterological Association, there were about 8000 vagotomy cases already done. So that within a period of five or ten years it is possible that we will know whether this simpler procedure will cause us to discard subtotal gastrectomy. After all, none of the operations we are doing for ulcer are ideal. An ulcer of the stomach is in the same category as subtotal thyroidectomy for hyperthyroidism. If the secretion of acid—which is certainly a potent factor in the genesis of ulcer but not the sole cause (because there are innumerable patients with hyperacidity who never develop an ulcer)—could be controlled medically, all these procedures we are doing at present will probably go into the discard.

# THE RESPONSE TO VAGOTOMY IN IDIOPATHIC ULCERATIVE COLITIS AND REGIONAL ENTERITIS\*

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## I. INTRODUCTION

AS ONE OF US REPORTED three years ago,<sup>1</sup> a study of experience with idiopathic ulcerative colitis at the University of Minnesota Hospitals for the 10 years ending January 1, 1944, revealed that the 57 patients treated expectantly and nonsurgically throughout, or until the situation had deteriorated to a point at which the outcome was hopeless before involving surgery, suffered a 28 per cent hospital mortality. On the other hand, the 25 subjected to elective ileostomy at a time when there was a reasonable choice suffered an 8 per cent mortality. Follow-up studies are incomplete, but show that more than half the survivors of expectant therapy from 1934 to 1936 were dead in 1946, while the great majority of those subjected to ileostomy in the ten-year period were living and well. Cancer in the remaining colon took a high enough toll to establish a policy of subsequent colectomy in all who needed ileostomy.<sup>2</sup>

In the period from 1944 to the fall of 1946, nearly all patients with ulcerative colitis were subjected to surgery, the hospital mortality remained below 10 per cent, and most patients returned to a nearly normal life. The utilization of a program of ileostomy, followed by colectomy with or without ileoproctostomy, thus was successful in terms of survival. On the other hand, it suffered from many disquieting facts. It was a confession of defeat in that nothing was done to salvage the diseased bowel, relying on removal of this bowel instead. It inflicted radical and somewhat deforming surgery on patients usually already somewhat emotionally unstable. It was not entirely free of annoying complications such as skin erosion and ascending ileitis. There was also the occasional catastrophe, no less disturbing because several occurred before surgery.

The need for a therapeutic method which might salvage the colon and avoid the extensive surgery was obvious. As recounted elsewhere, various members of the University Hospitals Staff have employed folic acid,<sup>3</sup> tetraethyl ammonium bromide,<sup>4</sup> and propyl thiouracil as suggested by Laurence Martin.<sup>5</sup> Employment of sulfathaladine<sup>6</sup> and of oral streptomycin seemed only rarely to help.

Employment of division of the vagus nerves was precipitated by a 20-year-old girl who had previously had all her colon and 5/6 of her ileum removed

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for colitis and ascending enteritis. Severe involvement of the remaining bowel failed to respond to all known conservative measures. Vagotomy was performed in October, 1946, at the suggestion of Dr. C. J. Watson of the Department of Medicine at the University of Minnesota. This procedure plus revision of ileostomy resulted in striking improvement. Other procedures have been required, but the patient maintains her weight and fair health at the present writing.

This result prompted us to employ vagotomy in four patients without other surgical therapy, all with mild disease, and to follow the group for six months before making the decision to use the procedure more extensively. At the end of this period, three of these patients presented normal proctoscopic findings, and the fourth was reported as "healed ulcerative colitis." All four had formed stools not oftener than twice a day.<sup>7</sup>

## II. PLAN OF STUDY

A more extensive study seemed imperative. The clinical studies were carried out by the present authors. Experimental animal work was performed by Lillihei, Dixon, Friesen, and Wangenstein, and is being separately reported by them.<sup>8</sup>

The plan of clinical study was formulated in an effort to evaluate every factor which might give some clues as to the mechanism of the effect and as to the selection of those cases which might benefit most by the procedure.

One week was employed for each series of studies. Such a series was prosecuted before surgery in those patients considered in condition to tolerate it, and again about a week after vagotomy. Patients were similarly re-studied every three months when possible until we were satisfied of the completeness of the division and the healing of the process. Thereafter patients have been seen less frequently, and the studies have been usually less varied.

Each series of studies included proctoscopic and Roentgen barium enema examination, a three-day observation with recording of size, consistency, and frequency of stools, laboratory checks of stools, transit time through the intestinal tract as measured first by charcoal ingestion, and later by barium meal and close following fluoroscopically, electrocardiograms, triple histamine gastric analysis,<sup>9</sup> 12 hour overnight gastric collection,<sup>10</sup> and Hollander insulin gastric analysis.<sup>11</sup>

## III. GENERAL MANAGEMENT OF PATIENTS

Many of the patients came to the University Hospitals in deteriorated or critical condition. One was transferred in hepatic failure and died before surgery could be considered in spite of vigorous therapy by both the Medical and Surgical services. This patient is not included in the series. One refused surgery and died six weeks later elsewhere. Because of the small reserve of these patients emphasized by these cases, all in the series were carefully prepared before embarking on surgery.

High caloric preparation is difficult in these cases, as increased feeding

has resulted in increased diarrhea, with water, salt, and protein loss. In many, therefore, preparation by the intravenous route has been necessary. Blood, plasma, and 10 to 20 per cent glucose solutions have been generously employed. We have customarily added insulin directly to the 15 or 20 per cent glucose in the amount of one unit to four grams, a measure which usually keeps the urine sugar free and the blood level in a normal range. By the use of the polyethylene tubing recommended by Grindlay,<sup>12</sup> it has been possible to deliver these concentrated sugar solutions directly into the superior vena cava by inserting 40-50 cm. of tubing through the antecubital vein; such a combination permits administration of 400-500 Gm. of glucose per 24 hours, and the same tubing has been employed as long as two weeks.

The employment of a long tube for suction in the terminal ileum has been employed several times in the past five years. It seems to have helped in preparation of some of the sickest cases, but unlike Grier Miller,<sup>13</sup> we have not been successful in keeping the colitis quiet except by oral starvation in addition to low ileac suction.

As previously reported, the early experience was that 30 per cent of patients with ulcerative colitis developed thrombosis or embolism in association with the performance of ileostomy; the routine administration of a single oral dose of dicumarol the night before surgery, however, resulted in a series of 20 consecutive cases with no thrombotic complications.<sup>14</sup> In the vagotomy series, after 20 cases without prophylaxis, embolus has occurred once. The patient recovered on anticoagulant therapy. The present plan, therefore, again calls for 200 mg. of dicumarol the night before surgery.

In cases requiring extensive intravenous preparation, it is now the practice to add heparin prophylactically to the infusion at the rate of 30-40 mg. every four hours.

The anesthesia to be employed is the choice of the anesthetist. We use extensively and with complete satisfaction a mixture of pentathol (25 mg/cc) and curare (five units/cc) intravenously, supplemented by a mixture of equal parts of nitrous oxide and oxygen by an intratracheal tube.<sup>15</sup> The intravenous infusion is given either through the cubital or the external jugular vein; the saphenous is never employed, for fear of thrombosis.

Our vagotomies have usually been performed through an incision in the left anterior seventh intercostal space. At the beginning of the study, a segment of the eighth rib was removed, but this resulted in excessive pain. The intercostal incision, with electrocoagulation of the exposed intercostal nerve, has left little postoperative discomfort. Omission of all sutures in the intercostal bundle seems also to have helped. Closure is accomplished with No. 2 chromatic catgut encircling the seventh and eighth ribs, and precise fine silk (1¼ lb. test) approximation of muscles and skin.

We routinely infiltrate the mediastinum with 10 cc. one per cent procaine before working in that area, a procedure resulting from one occurrence of cardiac arrest.



Postoperatively, gastric suction is now employed for one to two days, food thereafter being taken for a few days only as the patient hungers for it. Ambulation begins the day after surgery.

In seven patients, ileostomies had been performed in line with our former program, before vagotomy was employed. In one the ileostomy was closed at the same sitting, in another six weeks later. In the others it was learned that the ileostomy must be widely patent if static difficulties are to be avoided, as an intestine capable of overcoming moderate stenosis at an ileostomy becomes unable to do so following division of the vagi. One ileostomy made after vagotomy, with this in mind, has given no static difficulties.

It has been observed in several patients that the days immediately following vagotomy are marred by a profuse secretion of thin fluid from the intestine. This is not a serious problem except in the presence of a high ileostomy. In such cases the ileostomy drainage may exceed ten liters a day for several days. A sharp watch must be kept daily on serum sodium, potassium, and chloride levels, on the carbon dioxide combining power, and on the weight of the patient, and aberrations must be appropriately corrected at once. It is best to permit only soft or solid food by mouth, and to supply the fluid replacement only by the intravenous route.

#### IV. CLINICAL RESULTS OF VAGOTOMY

As reorted in the preliminary papers,<sup>7, 16</sup> most of the clinical results have been very encouraging, as the following case summaries indicate:

**Case 1.** A 23-year-old University student (777589) was admitted May 1, 1947, because of acute onset of abdominal pain. There was a history of resection of the terminal ileum and colon to the apex of the sigmoid and ileosigmoidostomy as a staged procedure three years earlier. He had been well in the interval, having two to three stools daily. Examination showed a very active proctitis and sigmoid colitis, a tender, spastic abdomen, a temperature varying from 100° to 104° F. Perforation of the remaining sigmoid colon seemed most likely on the basis of auscultatory and Roentgen findings. A long Wild<sup>17</sup> tube was placed in the small bowel, and penicillin, streptomycin, blood, and glucose were appropriately given. He was explored May 4, it being felt the perforation should have sealed in that time. In addition to the matted fresh adhesions and violent peritoneal reaction anticipated, the top two feet of the eight feet of free small bowel was found to be involved in a severe inflammatory process interpreted as regional enteritis. A double barreled ileostomy was done as low as possible.

His course thereafter was gratifying, and he went home May 22. Readmitted June 10 with dysfunction of the ileostomy and cramps which led to a diagnosis of extensive enteritis above the ileostomy. Proctoscopy showed almost complete healing, especially in the rectum. He was starved by mouth and fed formula into the distal ileostomy in preparation for surgery. On June 26 a transthoracic vagotomy was done, and at the same sitting the ileostomy and enough bowel to confirm the diagnosis were resected, and end-to-end anastomosis was done in thickened, angry looking ileum. The postoperative course was uneventful except for recurring pneumothorax which required repeated aspiration. Dismissed July 11, the patient gained 12 pounds the first week at home, 30 pounds the first month. He has remained well, has married, and works as an engineer six days a week. He has two small stools a day more formed than at any time since onset of his colitis.

**Case 2.** A six-year-old boy (763487), with a ten month story of bloody diarrhea, was admitted February 26, 1946. After diagnostic studies, a single barreled ileostomy was performed March 7. About 10 days later he developed evidence of dysfunction of the ileostomy in association with a flare-up of discharge from the colon. After a long try with conservative methods, he was re-explored April 30 and adhesions of omentum and ileum to transverse colon were freed, relieving ileac obstruction close to the ileostomy. Further trouble with the ileostomy led to resection of the ileostomy and 33 cm. of ileum, with a pathological diagnosis of ulcerative ileitis. Because of persistent active proctitis he was vagotomized on August 21, 1947. Repeat proctoscopic examination on September 16, 1947, showed total absence of the granularity, friability, and bleeding seen four weeks earlier, and the mucosa was described as normal. The ileostomy was closed September 18. This patient has gained weight and strength, goes to school without limitations of diet or activities, and has one or two formed stools daily. Proctoscopic examination March 5, 1948, showed normal bowel. Microscopic examination of the stool shows no pus, and there is a trace of blood on the benzidine test.

**Case 3.** A 19-year-old boy (781510) was transferred from another hospital on September 2, 1947, with a six-week story of high fever, abdominal cramps, and diarrhea running to 12 stools a day. He weighed 112 pounds, in contrast to his usual weight of 152 pounds one year before. He was emaciated but had been freely transfused. Films from the other hospital showed diffuse acute enterocolitis, with classical "string sign" in several places from jejunum to colon as well as colitis. Oral feeding seemed out of the question; after two days of 15 per cent glucose and blood by vein, a transthoracic vagotomy was done. Penicillin and streptomycin were given the first few days. The patient had no stools the first four days after operation, and was given mineral oil, following which liquid stools appeared until September 14, when formed stools appeared. He has had one or two formed stools a day since that time, except for three occasions of one day of diarrhea. He gained 35 pounds in the first three months and is again a student at the University.

Despite such striking cases the vagaries of idiopathic colitis cause us to draw conclusions only with misgivings. That many other factors than the division of the vagi may have played a part in our results can be emphasized by one case:

**Case 4.** A 47-year-old woman (778555) was admitted from another hospital on February 14, 1948. She had had mucous colitis for 20 years, with superimposed acute ulcerative colitis of two months' duration, diagnosed proctoscopically, which had depleted her hemoglobin and serum protein stores. Oral feeding was totally inadequate and tube feeding not tolerated. A polyethylene tube was placed on February 22 into the superior vena cava through the right antecubital vein, through which one liter of 20 per cent glucose covered by insulin was given daily. Blood and plasma were given in other veins. She developed recurrent deep femoral thrombophlebitis which was treated by heparin. She took no food by mouth until after removal of the polythene tube on February 28. She regained strength rapidly in the next few days. Proctoscopy on March 3, 1948 showed normal mucosa. The patient has had one formed stool a day since that time. Vagotomy was not done because of a left eventration of the diaphragm, deep phlebitis, and complete anatomical recovery from her only attack, which had been heralded by extreme emotional strain not likely to recur.

There have been four deaths in the group of patients for whom vagotomy had been planned or was actually performed. The first occurred in a woman who was admitted in acute hepatic failure and who died in coma despite our efforts to prepare her for surgery. The second was a 32-year-old patient who had had colectomy and ileosigmoidostomy four years earlier. As the mediastinal pleura was being opened to perform vagotomy for recurrent proctitis,

cardiac arrest occurred. It was converted to fibrillation under massage and then to normal rhythm by intraventricular procaine injection. The vagi were not divided. She died, apparently of ventricular fibrillation, eight days later.

Our third death occurred as follows:

Case 5. A 32-year-old housewife (UH 776892) has ileostomy performed on 4/21/47 as a desperate final gesture for a very active generalized colitis. She had had elective gynecologic surgery elsewhere eight months earlier despite the colitis. Following ileostomy she regained strength and was allowed to go home. She returned on 10/9/47 with abdominal cramps and profuse bloody purulent drainage from the rectum. Transthoracic vagotomy was done 10/28/47. She did not respond well, although the rectal drainage did decrease. Gradual decline followed, and she died in hepatic failure, 1/15/48. Autopsy showed remains of a very old abscess involving the sigmoid colon and three segments of ileum proximal to the ileostomy, with a large fistula into each, and acute liver atrophy. The fistulas were thought to antedate ileostomy.

This woman might not have died if we had attacked the bowel when her condition was fair. Although one barium enema examination has been since re-interpreted to show an ileosigmoid fistula, this situation was not recognized during life, as it might have been if we had not employed transthoracic vagotomy.

Our fourth death appears to have occurred from other causes:

Case 6. A 27-year-old man (UH 780469) was admitted 8/12/47 with a seven year history of colitis. His home physician had already performed ileostomy and colectomy, leaving a rectum which was involved with active proctitis. His course had been complicated by repeated bouts of ileac obstruction for which he had had two explorations with enterolysis. The patient had a burning desire to have the ileostomy closed, and vagotomy was hesitantly suggested and accepted only because it offered some hope in this direction. We considered combining enterolysis, revision of the ileostomy, and subdiaphragmatic vagotomy, but there were numerous stitch abscesses in the several abdominal scars. After transthoracic vagotomy, the rectum showed some improvement before dismissal. The patient refused to return for follow-up because of resentment against use of gastric analyses. Recurrent bouts of obstruction occurred some months later. A strangulation obstruction was surgically relieved by the home physician on one occasion. He died following another exploration for recurrent obstruction at a third hospital in April, 1947. The rectal discharge is reported by his home physician to have decreased considerably in the last few months.

Twenty-eight cases comprise the series on whom vagotomy has been performed. Two were done through abdominal incisions, one to exclude the diagnosis of carcinoma of the sigmoid colon after barium could not be pushed past this point, the other because of an old subscapular abscess. The others have been done transthoracically to avoid all possible manipulation of the colon. One patient had had only a functional diarrhea (12x daily) for four years without demonstrable pathologic changes. She has had an excellent result, now usually having one or two formed stools a day. Two vagotomies for colitis are too recent for full evaluation and are not included; both show mucosal improvement.

Therefore, 25 cases of vagotomy on patients with ulcerative colitis are available for follow-up consideration. In 16 of these, vagotomy was the only surgical procedure (see Table I). Six of these latter have become asymptomatic.

matic, i.e., they have no more than two stools a day, the stools are soft formed and free of gross blood, pus, and mucus, and they have no gastric distention or abdominal discomfort.

Four of these 16 cases are not asymptomatic but are improved; one of these is so listed because she was committed to a State Hospital and there

TABLE I.—Clinical Results of Vagotomy in Ulcerative Colitis and Enteritis

	Asympt.	Improv.	Not Improv.	Worse
Vagot. alone .....	6	4	5	11
Vagot. with ileost. ....	32	33	—	14
Vagot. with previous anastomosis .....	15	—	16	—
Totals .....	10	7	6	2

- 1 Required emergency ileostomy after barium enema three months later.
- 2 One had both sigmoiditis and high regional enteritis; the ileostomy was closed at the same sitting. One had enteritis above the ileostomy. One had high enteritis and proctitis; the ileostomy was closed in four weeks, at which time the rectum had healed.
- 3 Two had high enteritis; one proctitis.
- 4 Died at three months of multiple fistulization from high ileum to sigmoid thought at autopsy to pre-date surgery.
- 5 Massive hemorrhage from enteritis above ileoproctostomy.
- 6 Previous ileoanal "pull through" with diseased ileum.

has been no success in gaining information as yet; there had been reduction in stools in the first two weeks. This woman was seen in June, 1948, and is symptom free. Another is continuing to improve, but the period of observation is only nine weeks. A third is showing progressive roentgen-ray and clinical improvement at 18 months; the proctoscopic appearance is normal. The fourth has had improvement in symptoms and loss of most of the inflammatory polyps in the colon, but still has occasional days with as many as four stools.

The disease may be classified according to the type of involvement. As Bargen has pointed out, there may be maximal involvement in the rectum with apparent spread from this area to the rest of the colon, and perhaps to

TABLE II.—Type and Extent of Disease in Patients Subjected to Vagotomy

	—Universal Colitis—		—Regional Colitis—	
	Number of Cases	Percent Improved	Number of Cases	Percent Improved
Ileum involved .....	10	70	4	100
Ileum free .....	10	60	1	0

the ileum, the universal type, or the segmental or regional types of colitis or enterocolitis, of which regional enteritis is a sample. Twenty of the 25 cases were universal in type, and about half of all the cases had ileac involvement. There seemed to be no definite relation between the type and extent of disease to the response to vagotomy (Table 2).

Five of the cases subjected to vagotomy alone are unimproved. One 12-year-old boy had *endameba histolytica* in the stool; he has two to three stools a day when he can be kept from popcorn and peanuts. Another is an extremely uncooperative and high-strung boy of 17 who came with 18 stools

a day and is now down to nine; he is listed as improved but has refused to return for evaluation. Two patients were well for many months only to suffer a recurrence of diarrhea.

One patient who had vagotomy performed to control massive bleeding progressed well for three months only to suffer recurrent activation requiring emergency ileostomy.

Nine patients who had had ileostomy or some form of ileoproctostomy were subjected to vagotomy. This was done for relief of higher regional enteritis or ascending enteritis in five cases, for proctitis in one case, for recurrent colitis in one, for involvement just above a low ileoproctostomy in one, and for involvement of ileum previously used for an anal "pull through" in one.

The last case mentioned is unimproved; he still presents actively diseased ileum on proctoscopy, although the stools are nine instead of 15 to 18 daily. The one who had vagotomy for an exacerbation after ileostomy is the third death listed above.

Three of our patients have suffered recurrent bouts after vagotomy.

**Case 7.** A 47-year-old woman (620076), with colitis dating from 1933, came to us December 5, 1946. She had had spells of diarrhea and cramps twice a year for years, with vomiting and distention. These bouts lasted two or three days, but distention and abdominal discomfort were never entirely absent. Proctoscopic examination showed moderate low-grade involvement most marked in the rectum. Barium enema showed nothing abnormal except some mucosal changes in the low sigmoid. Following vagotomy she suffered diarrhea for a few days, then enjoyed normal bowel function and presented a normal proctoscopic picture until May, 1948, when she developed two or three stools a day, liquid half the time. No abdominal discomfort was noted. No gross blood or pus was seen in the stool. Proctoscopic examination shows only very slight hyperemia. Barium enema shows only the slight atony usually seen after vagotomy. Bland diet suggested.

**Case 8.** A 32-year-old woman (782759), with colitis the preceding two years, was admitted October 28, 1947, because of massive hemorrhage and shock. This was treated expectantly and subsided. There were then two to four liquid to soft stools daily. Study showed involvement of the rectal mucosa of moderate degree, and loss of haustration of the entire colon. After vagotomy her stools returned to normal consistency and once daily, and the proctoscopic appearance became almost normal. Follow-up studies in early March, 1948, showed active disease in the rectum. Unfortunately a barium enema was performed at this time. A severe exacerbation occurred during which the situation became so critical that an emergency ileostomy was performed. Recovery thereafter was slow, but progressive.

**Case 9.** A 56-year-old woman (670169), with colitis dating from 1933, came to us September 21, 1947. She had had two to three formed or liquid stools daily for years. She had been subject to severe bouts of bloody diarrhea and abdominal cramps and fever, coming in the early summer each year. She presented an active proctitis with pus and mucus present. Roentgen study showed moderate colitis and low ileitis. After vagotomy she slowly improved, and in December, 1947, was having one formed stool a day, presented a normal roentgen study on the colon and much improved proctoscopic appearance. About March 15, 1948, she began to have four to five liquid stools a day, with extreme urgency. This bout is less severe than before vagotomy, and is not accompanied by abdominal discomfort. Examination May 18, 1948, shows active ulcerative colitis involving the upper

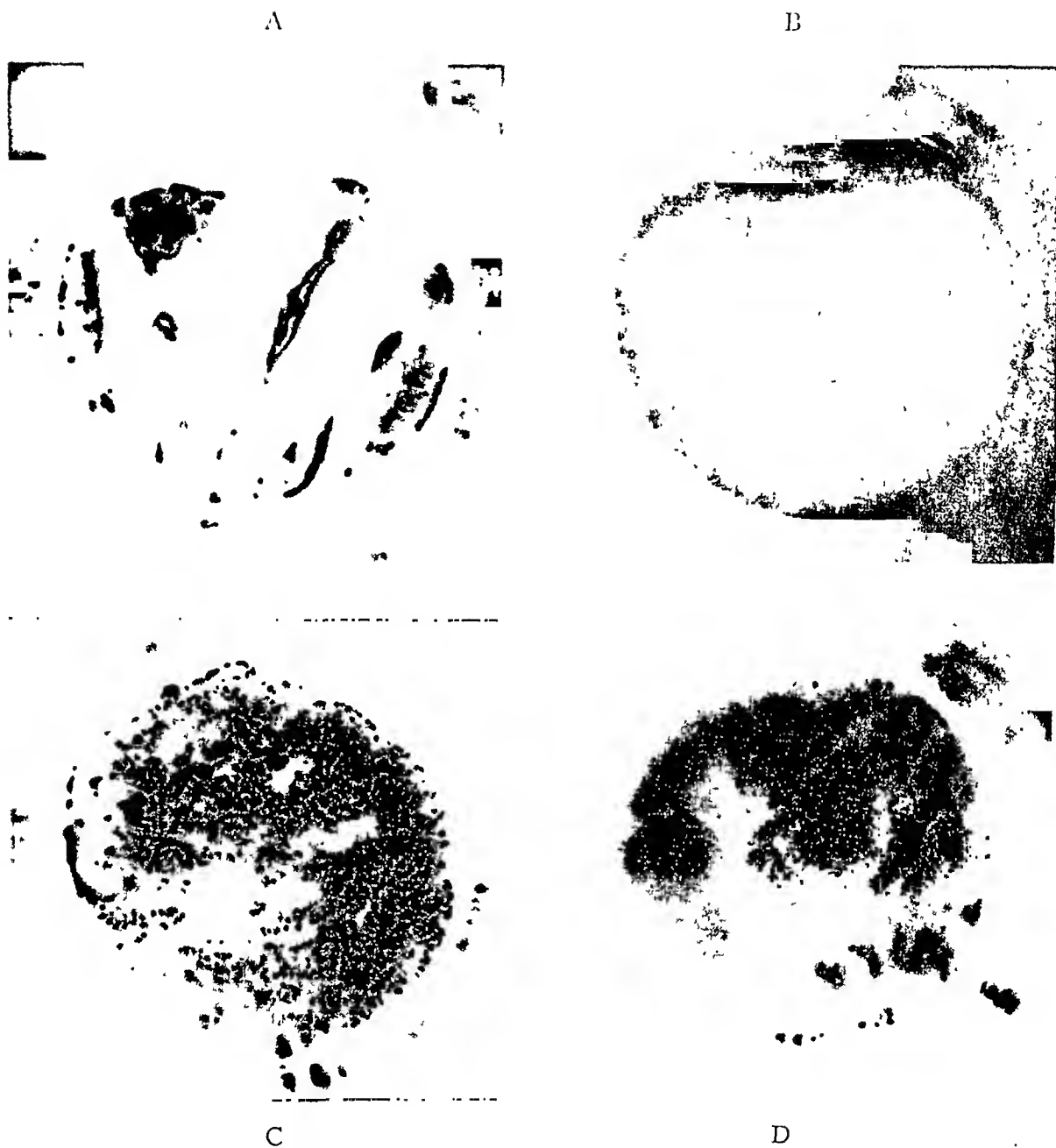


PLATE I.—Photographs of the rectosigmoid mucosa in ulcerative colitis.

- A. Same patient as Figure 1, before surgery.
- B. Same patient six weeks after vagotomy.
- C. Patient 784756, a 17-year-old girl with a two-year history of colitis, before surgery.
- D. Same as C, three months after vagotomy. The patient had gained 30 pounds.



rectum and lower sigmoid. The patient was symptom free and the proctoscopic appearance normal in July.

*Weight.* The average weight gain from the time of vagotomy to the present is 15 per cent. One of those gaining best is classed for other reasons as unimproved. Maximal weight gain occurred in a 24-year-old boy with a seven-year history of colitis and a very spastic, rigid colon. His weight rose from 39 Kg. to 64 Kg. in the three months after vagotomy. He is asymptomatic.

*Proctoscopic changes.* Proctoscopic changes could be evaluated in 20 cases. In four there were no abnormalities here at any time. In four more, an actively diseased mucosa has assumed a normal appearance. In seven there is definite improvement without complete healing. In two, definite disease in the rectal mucosa has remained unaltered. In three cases the mucosa looks more diseased than before vagotomy; two of these are in exacerbations occurring after the procedure.

The majority of those patients who had diseased rectums present at examination have shown definite improvement in the proctoscopic appearance within two weeks after vagotomy. In most, this improvement continued over a period of months, being particularly slow in those with long-standing colitis or with marked fibrosis.

Some of these changes were very striking, as shown in Plate I.

*Roentgen changes.* In all but one of those cases in which abnormal roentgen findings were present initially and in which serial barium enema roentgen studies were possible, improvement followed vagotomy. There was only one instance in which the appearance returned entirely to normal; this patient (670169) developed an exacerbation six months after vagotomy. In one case, spasm appeared to be more marked in the colon after vagotomy than before (782759). This patient later suffered an exacerbation also.

In general, improvement has been progressive to such a degree that a status approaching normal is ultimately to be anticipated. Such a change is indicated in the roentgenograms of Figure 1.

There was throughout the series a tendency toward less spasm after division of the vagi. This tendency was also observed in a group of patients vagotomized for duodenal ulcer at the Minneapolis General Hospital.

*Stool studies.* Stool studies have included repeated search for *endameba histolytica*, pus, and mucus by the microscope, and for blood by the benzidine and guaiac tests. Blood, pus, and mucus have been found with less frequency after vagotomy in half the cases, but there are none free of all these constituents. Absence of gross blood, pus, and mucus has seemed usually to follow operation.

*Retention.* Gastric retention required later gastroenterostomy in one case. One or two others complained of bloating and sour eructation for a short time only.

#### V. RESULTS OF SPECIAL STUDIES

*Gastric acids.* Triple histamine (Lannin) analyses were changed by vagotomy more than expected on the basis of the studies of others,<sup>18, 10</sup> in



A



B



FIG. 1.—Barium enema Roentgenograms of case 784831—an 18-year-old boy with a three-year history of colitis. (a.) Filled colon prior to surgery. (b.) Evacuation film prior to surgery.

C



D



FIG. 1.—(c) Filled colon eight weeks after vagotomy. (d.) Evacuation film after vagotomy.—Note decrease in spasm and return of haustral and mucosal markings. The patient had gained twenty pounds in this period.

that three patients became totally achlorhydric. Other than these, there was little change except for a moderate tendency to reduction in the free acid response.

Our results with the 12-hour overnight collection used by Dragstedt suggests that the large preoperative volumes seen by him were related to the gastroduodenal ulcer picture. The mean preoperative volume was 440 cc., with no free acid in two-thirds of the cases. The mean postoperative value was 210 cc. with no free acid in a slightly higher fraction.

The Hollander insulin gastric analysis was performed by giving one-half unit of insulin per kilogram of body weight subcutaneously, collecting gastric juice continuously for two hours, with separation into 15-minute samples. The test was accepted as implying complete division only if there was no rise in free acid with a blood sugar level below 45 mg. per cent. In most instances this was performed two or more times in the postoperative period, and all tests were satisfactory before division of the vagi was considered complete.

The first patient presented evidence of incomplete division, and had the rest of the fibers divided at a second procedure. This did not seem further to improve her status.

Three other patients present unsatisfactory evidence of complete division in that there is an acid response to the insulin test. One had very minimal universal colitis and has been followed for 16 months. Two had regional enterocolitis (one a classical regional enteritis involving high ileum, jejunum, and duodenum, as well as sigmoid). All three are totally asymptomatic. Each of the patients suffering recurrent bouts of colitis presents insulin test evidence of complete division of the vagi (two on one test only, as yet).

*Transit times.* The time required for transit of material through the intestinal tract has been broken down insofar as possible. It is now common knowledge that there is delay in gastric emptying after vagotomy. An attempt was made to determine whether or not there is a retardation in transit through the small intestine and the colon in these cases.

To study the small intestine, the moment of entry of barium into the duodenum was noted as often as possible in gastro-intestinal stasis studies.\* Fluoroscopic follow-up studies were so spaced as to try to estimate the time of entry into the cecum. In only eight cases was it possible to time these occurrences both before and after vagotomy. The mean small bowel passage time was 3.5 hours before operation and 7.5 hours afterward. In no instance did passage fail to be slowed after surgery.

It is recognized that slower emptying of the stomach may contribute to this lessening of speed of passage in the small bowel. As a means of evaluating the intrinsic activity of the ileum, long nasal tubes were passed into the ileum for recording of activity by balloon and tambour. In view of our total failure to pass such a tube out of the stomach after vagotomy, it was left in during

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\* The authors wish to express their profound gratitude to Dr. L. G. Rigler and his staff for their patient cooperation in the frequently exasperating studies entailed.

the procedure and convalescence for the purpose of repeating the studies after vagotomy. The results are not entirely conclusive as yet, but such observations as have been made suggest reduced tone and activity after section of the vagi.

Transit through the colon was more difficult to evaluate, and in only three instances was it possible to time arrival at cecum and rectum both before and after surgery. The mean colon transit time before vagotomy was 3.1 hours, afterward it was 11.3 hours.

An effort was made to judge intestinal activity by checking the time required to pass six Gm. of charcoal taken orally at 6 P.M. There were 14 cases without ileostomy or resection in which comparisons were made. The relative infrequency of stools in the postoperative observation in most patients distorts the picture in one direction, and the occasional profuse secretion in the other. The means were 18 hours before and 23.3 hours after vagotomy.

*Electrocardiographic observations.* At first it was thought that persistent changes followed vagotomy, but these appear to be no more common after this than after other procedures.

*Laboratory observations.* With the observation of striking improvement in the first cases, Lillehei, Dixon, Friesen, and Wangenstein<sup>18</sup> directed the experiments they had already been performing on the origins of colitis toward the possible role of autonomic innervation. They confirmed Lium's<sup>19</sup> finding of usually fatal bloody purulent diarrhea in dogs after removal of the mesenteric ganglia. They found, however, that this effect does not follow if vagotomy is done at the same sitting.

*Emotional changes and the rectal mucosa.* Wolf and Andrus have reported that intense swelling and engorgement occur in the gastric mucosa of man in the course of strong emotional reactions, such as anger. They furthermore noted this reaction of the mucosa to be lost after division of the vagi. Holman has found that essentially the same responses to emotional reaction occur in the terminal ileum and cecum, and it occurred to us together that the same changes might be studied in the rectums of patients suffering from ulcerative colitis.

That vagal influences upon the sigmoid and rectum exist would at first seem very unlikely. Degeneration studies after division of the vagi in experimental animals indicate that vagal fibers extend only to the midportion of the colon,<sup>22</sup> and that division of fibers in the sacral outflow results in similar degeneration in nerves in the left colon.

The finding of rapid rectal healing after vagotomy for ulcerative proctitis in a patient with ileostomy would suggest some more direct effect than change in the character of the contents coming from above.

Experimental work by Almy and Tulin<sup>23</sup> has shown that severe pain produces increased motor activity in the rectum and that emotional responses produce in some normal people an engorgement of the mucosa and increased secretion.

Thus far, two patients have been studied before and after vagotomy for colitis.

**Case 10.** A 30-year-old housewife (MGH 1478A-48) presented a seven-year history of colitis, and was admitted in February, 1948, because of an exacerbation and multiple huge abscesses on the back, buttock, and thigh. After drainage of these and dietary and general management, the colitis subsided. Proctoscopic examination, April 28, with the patient comfortable in the Sims position, showed only very minimal engorgement of the moderately granular mucosa when pain was produced by probing and repacking the abscess pockets. Discussion of her sorest subject, prolonged separation from her children, resulted in an immediate tense engorgement of the mucosa, excessive secretion of watery fluid, and in the sudden appearance of four or five superficial hemorrhages on the surface under observation. With change of the topic to other subjects, the engorgement disappeared almost as rapidly as it had come.

This patient was re-examined in the same manner May 12, 1948, four days after subdiaphragmatic vagotomy. At this time there was a periodic color change not noted before vagotomy in this or other patients. Most of the time the mucosa was pale, but every three minutes it became pinker for  $\frac{1}{2}$  minute, without engorgement. Discussion of her children and her separation from them produced none of the pre-vagotomy engorgement, and, even on the disclosure to the patient that a large new abscess in the left buttock would require more surgery and a longer stay away from her children, there was no change.

**Case 11.** A 19-year-old boy (MGH 3345 A-48) with a five-year history was similarly observed. Several items of conversation were each found to be associated with visible emotional disturbance and engorgement of the mucosa. The changes were definite, but less striking than in the first patient. In discussing his relations with his sister, three superficial petechial hemorrhages appeared in addition to engorgement. This patient had active ulceration present at this time.

On May 17, 1948, five days after vagotomy, the mucosa already looked paler, although it traumatized very easily. Review of the above topics of conversation produced no definite changes in vascularity or engorgement. We were not entirely satisfied that he had been as emotionally upset as the first patient or as before surgery.

Five additional colitis patients have been examined in this fashion, but unfortunately the vagotomy had already been performed before such observations were conceived. In three there was definitely no engorgement or color change on discussing subjects known to be very sensitive to the patients. In another there was one definite increase in color, not while on a sore subject and not associated with engorgement. In the fifth there was a periodic blush of the mucosa, unrelated in time to the subjects which bothered the patient.

Two patients subjected to vagotomy for duodenal ulcer were similarly studied before and after surgery. Engorgement was minimal but definite on discussion of painful subjects before surgery, and absent afterward, although one of the patients showed a periodic pinking not correlated to conversation or pulse rate.

These observations seem definite, even though we appreciate that most of these patients are much less tense and excitable after vagotomy than when they still had pain or other symptoms of colitis or duodenal ulcer.

*The gastroenteric reflex.* In two patients there was a definite history of urgency to defecate on partaking of food, with relief from this annoying difficulty after vagotomy. This has not been felt to mean abolition of the gastroenteric reflex beyond doubt because the frequency of stools had been so much

reduced by the procedure. Studies on changes in small bowel motility by the inlying balloon method are as yet inconclusive on this point.

#### VI. PREOPERATIVE ESTIMATE OF EFFECTIVENESS OF VAGOTOMY

Since some of these patients have done very well and others have not, we have critically reviewed all available evidence in an effort to delineate the factors either indicating or contra-indicating employment of vagotomy.

It at first seemed that early cases responded more favorably than those of many years' duration. Charting of clinical results against duration shows no correlation whatsoever.

The degree of fibrosis does seem to play a part. Almost total loss of haustral markings, and of distensibility, both by proctoscopic and by radiological estimates, leads regularly to a poor result. Those with an estimated three-quarter loss of elasticity derived slightly less consistent good results than those with lesser degrees of change. Most of the excellent results were achieved in cases with little or no limitation of elasticity.

This observation has indicated also that patients with marked loss of colic elasticity are slower to improve after vagotomy than those without such loss.

It would seem that the maximal chance of a good end result should be found in those cases vagotomized in the first few weeks of the disease, before fibrosis is a factor.

#### VII. COMMENT

One of the disturbing aspects of this study is the fear that carcinoma of the colon will develop with the 14 per cent frequency previously reported in old cases on long follow-up. In many cases the bowel has returned far enough toward normal to cause us to hope that this high incidence would no longer prevail. In any case, the present course, with careful observation, seems the only course allowing a solution to the problem.

The mechanism by which vagal section changes the course of idiopathic ulcerative colitis is unsettled. The reduction in colic tone which regularly follows vagotomy would suggest that relief of spasm is important. The rapid response in some cases with ileostomy above suggests the mechanism is not through some change in intestinal juices coming from above. That some change in lysozyme activity is important is suspected by Holman and is now under study by that group.<sup>21</sup>

It is difficult to ignore the possibility that vagal innervation extends as far as the anus; at least the results appear *as if* this were the case. Much of the benefit may then accrue from protection of the mucosa from the reflex effects of the violent emotional stress to which these patients are so subject.

A definite answer to this problem is not possible in the present state of our knowledge.

#### CONCLUSIONS

1. Idiopathic ulcerative colitis responds favorably in most cases to division of the vagus nerves. Regional enteritis has also responded.
2. The response is usually most marked and most prompt in cases in which there is not great loss of distensibility of the colic wall.

3. Patients with extensive fibrosis in the bowel wall, as a result of colitis, occasionally take many months to improve after vagotomy.
4. The mechanism of this effect is in doubt, but the reduction in mucosal vascular response to intense emotion and the relief of enteric spasm seem to be important.
5. The effect of vagotomy on the vascular response of the rectum to strong emotion is *as if* vagal innervation includes the rectum.

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DISCUSSION.—DR. HENRY W. CAVE, New York: We all know that in ulcerative colitis there is marked disturbance of the motor mechanism of the colon. On the right side of the colon there is hypomotility with resultant stasis and a feeling of fullness in the right side. In the left colon, from the midcolon down, we will say, there is marked hypermotility with marked irritability and resultant diarrhea. Vagal section, as suggested by Dr. Dennis in this excellent presentation, may correct this imbalance. I should like to ask Dr. Dennis the average duration of illness in these cases prior to vagal section. We all know that this disease is a cyclic recurring disease; there is first a stage of acute activity, a second phase of convalescence, a stage of quiescence, and a fourth stage of recurrence of reactivation of the process in the colon. We have seen many cases that have remained quiescent no matter what was done; whether treated medically or otherwise, they have remained quiescent for periods up to two years. I think a good many of Dr. Dennis' cases were of long standing, and it seems to me that where there are irreversible changes with pseudopolypoid degeneration, infiltration in the colonic wall, it is hard to believe that a vagal section can cure that patient of his disease. I am sure when they get to that stage, with thickening, loss of laustral markings, and the disease is irreversible, nothing will do any good except removal, and I want to bring out one particular point in the question of removal of the colon; that is, the question of incidence of malignancy in the colons and rectums that are left in. In our series, seven developed carcinoma. I understand that Dr. Cattell at the Lahey Clinic has an incidence of 14 per cent development of cancer in the segment of the colon or rectum left in place. I feel that one is committed to removal of the colon when it gets to the point of possible malignancy on the basis of 14 per cent incidence in the disease.

I should like to ask Dr. Dennis one more question. After vagal section does the temperature subside and does the spasm abate. I think that is important in these cases. As he says, he has been doing the operation only since October, 1946, and the time is too short to evaluate properly the results of his work.

DR. FRANK H. LAHEY, Boston: Anything that can improve our methods of handling ulcerative colitis is certainly welcome to those of us who have to deal with these cases in considerable numbers. It is a distressing disease of unknown origin, unpredictable as to when the acute critical stages arise, and with it there is associated a very definitely high mortality. I wish particularly to compliment the author of the paper on the suggestion that there is another method of treatment to be applied to this distressing disease. I want again to call the attention of this audience to one fact, and I want to be sure that this method does not alter the progress we have made with this disease, and I am quite sure it will not. I would like to say that we must not lose sight of two or three very important things in connection with ulcerative colitis. One is, how quickly an acute stage of the disease can appear and how quickly the patient can die in it. Unless you have seen a large number of patients you may not realize that the disease may become acute overnight, and the patient can die within a week; they can die from intoxication, perforation or hemorrhage.

That again brings up a very important point—when to do an ileostomy. We have had an opportunity to compare two good-sized series of ileostomies in patients with ulcerative colitis. There were 80 cases in each group. The mortality in the first group was 22 per cent; in the last group, in the neighborhood of 5 per cent. That is due to just one thing—the performance of the ileostomy at an early enough date. This is in no way a criticism of the form of treatment; it is a warning lest as the result of delay we get back to the point where we again have a 22 per cent mortality in ileostomies. Another thing we must remember is that when these patients are hemorrhaging from an ulcerating colon they can bleed faster than blood can be put into them and they may require an emergency colectomy. I am particularly

anxious to stress these points lest we delay unduly as we try out this method, but I welcome it as another method of treating this very distressing disease.

DR. C. W. HOLMAN, New York: I should like to summarize our preliminary findings in a patient with ulcerative colitis whom we subjected to vagotomy. We are now rather cautious about interpreting our early findings as a result of this case. The patient was a young man admitted to the hospital because of a large prolapse of the right half of the colon and ileum, following ileostomy performed about a year and a half before. He had had ulcerative colitis for two years prior to operation. In this patient, the large amount of exposed visible bowel provided an excellent opportunity to observe the effect of vagotomy and the influence of various stimuli.

(slides) Before operation you see this prolapse, approximating at times the size of a football. Administration of physostigmine produced hypermotility and slight increase in contractility and vascularity. Dr. Grace and Dr. Wolf found that psychic stimuli, particularly anger, would make the bowel contract and become hypermotile, the vascularity would increase, and at times even ulcerations developed. A trans-thoracic vagotomy was done, apparently a complete one, as judged from the result of an insulin test. Four days after vagotomy the bowel had lost its motility and no longer responded to psychic stimuli. There was no longer an increase in vascularity. But during the next two weeks this changed, so that eventually he developed increase in motility, increase in vascularity and increase in ulceration as a result of psychic stimuli. Coincidentally, he developed bloody and mucus discharges from the rectum and all evidences of an increase of activity in the lesion of the large bowel. I might say that this postoperative course was complicated by disturbances in motility of the upper gastro-intestinal tract that made feeding difficult, which might very well be a factor in the unsatisfactory result following vagotomy in this patient.

DR. CLARENCE DENNIS, St. Paul (closing): I want to thank all the discussors. The average duration of the disease before vagotomy varied a great deal. The earliest case was done about four weeks after onset of the disease; that is the one with such a good result that I outlined to you. The longest that I can think of at the moment was 14 years; although Dr. Zierold, who is a member of this group has, I believe, a patient who had the disease for 19 years, who had a good deal of improvement only after several months following operation.

With regard to the development of quiescence in the disease after any sort of manipulation, I think it should be borne in mind that this is always a possibility. Dr. Bergen has seen several of these patients with me, and we have discussed them in considerable detail. He tells me he has had two patients with acute ulcerative colitis, on whom he put Boothby masks, with complete subsidence of the disease, and he sent the patient home asymptomatic and with apparently normal proctoscopic findings. He said it looked like a beautiful thing, but never would work again, and it is worth pointing out that this can occur. We have one patient who came in with an acute ulcerative colitis of a few weeks' duration, who was treated with intravenous infusions for a week by a polythene tube in the vena cava, who responded beautifully without surgery and has, at the present time, normal proctoscopic findings and no symptoms.

With regard to Dr. Cave's question about pseudo-polyps, we have only one patient with pseudo-polyps upon whom vagotomy has been performed. The patient did not like the idea of having an ileostomy, and vagotomy was second choice. Vagotomy was performed; she came back in four or five months with the thought in mind that we could now do a colectomy and low anastomosis. On proctoscopic examination the polyps had disappeared. For this reason she has had no further



surgery in spite of the reappearance of a single polyp in the last two or three months. We thought it better to follow this patient to see what happened.

I agree with Dr. Cave that where there are advanced changes that would suggest the occurrence of carcinoma, it would be unwise to do a vagotomy, thus letting more time go by for carcinoma to become fully established.

With regard to the length of time before fever and spasm disappear, there has been a good deal of variation. Most patients with fever had acute processes and, in most cases, the fever disappeared in three or four days. The disappearance of spasm was apparently very rapid, just as Dr. Dragstedt has pointed out in patients with duodenal ulcer.

Dr. Lahey mentioned the rapidity with which the process can develop. Two of our patients had very acute processes, and vagotomies were done in situations in which we felt that either conservatism or ileostomy would certainly result in the loss of the patient. Both have done very nicely. I agree with Dr. Holman that a much longer period of observation is necessary before any definite conclusion with regard to emotional responses can be formed.

# PHARMACOLOGIC FACTORS INFLUENCING COLLATERAL RESPIRATION; POSSIBLE RELATION TO THE ETIOLOGY OF PULMONARY COMPLICATIONS\*†

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In 1930 VAN ALLEN, LINDSKOG AND RICHTER<sup>1</sup> presented experimental and clinical evidence to show that the pulmonary segments of man and certain animals are not isolated units or end structures from the standpoint of their ventilatory function. These authors demonstrated experimentally, in vivo and vitro, that an obstructed segmental division of a lobe can obtain air from adjacent, freely ventilated segments. To this function of the obstructed pulmonary segment the term collateral respiration was given. (Fig. 1.)

Subsequently, the same investigators and their co-workers demonstrated that an obstructed segment may breathe through collateral respiratory channels at least 10% as much air as would normally flow through direct bronchial channels, and that the volume-flow of collateral air varies directly and proportionately, within certain limits, with the depth of respiration (tidal volume).<sup>2</sup> It was also shown that the volume-flow of collateral air is decreased by phrenicectomy and by tight abdominal binders and that when unobstructed segments of a lobe are inflamed, swollen or consolidated from chemical or bacterial action, collateral respiration may be interfered with sufficiently to allow atelectasis to develop in the obstructed portions.<sup>3</sup>

By demonstrating the collateral passage of liquids and particulate matter it seemed certain that the major part of collateral respiration occurs through the pores of Kohn.<sup>4</sup> Convincing histologic evidence of the existence of these interalveolar communications in normal mammalian lungs was advanced by Ogawa<sup>5</sup> and more recently by Loosli.<sup>6</sup>

It is evident from these studies that collateral respiration has much the same economic role in the operation of the bronchial tree as collateral circulation has in that of the vascular system, for both act to conserve the function of the parts which have become obstructed. Collateral respiration minimizes the incidence of segmental atelectasis and renders assistance in bronchoelimination.<sup>7</sup> Because of the small pressure gradients involved, the mechanism is highly susceptible to interruption by many factors.

This physiologic collateral mechanism seems to fit well into the widely accepted obstructive theory for the etiology of postoperative pulmonary atelectasis, because the mechanical factors deemed most significant in its production,

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† Read before the American Surgical Association, May 28, 1948.

namely, pulmonary hypoventilation secondary to rigidity of abdominal muscles and wound pain, restraining dressings, pneumoperitoneum, and intestinal distention with resultant elevation of the diaphragm also interfere with collateral respiration.

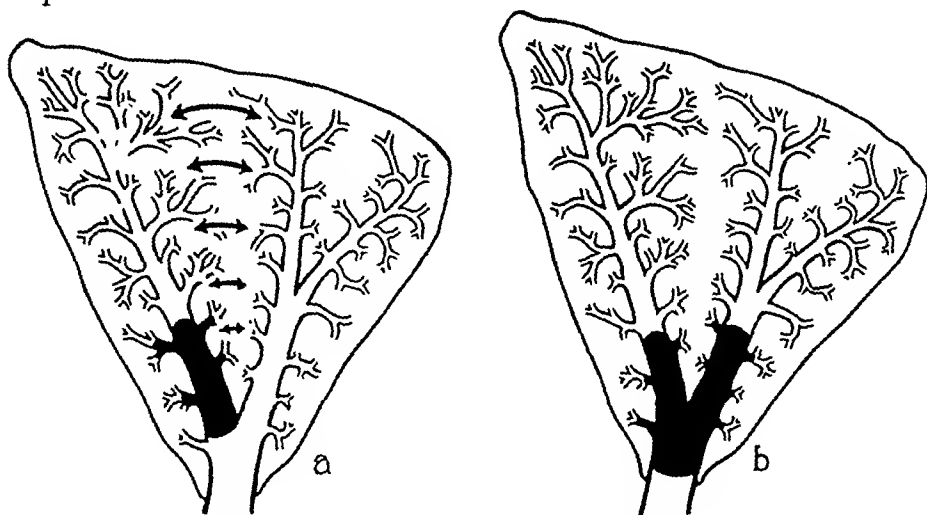


FIG. 1.—Diagram showing types of bronchial obstruction. (a) Lobular or segmental, which permits collateral respiration. (b) Lobar, which prevents collateral respiration.

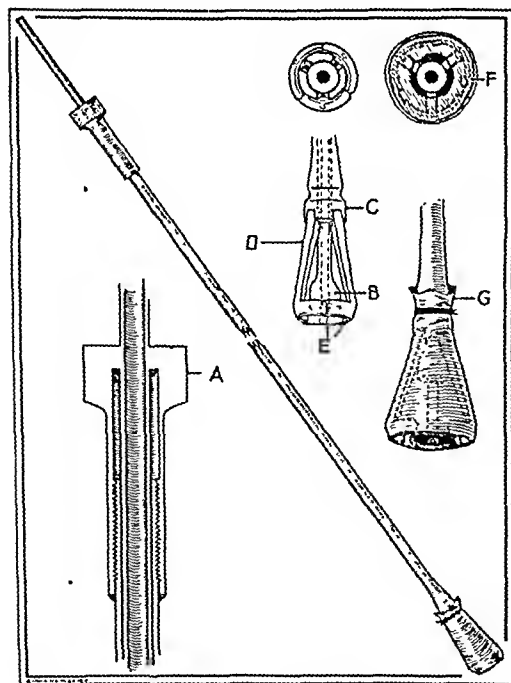


FIG. 2.—Diagrammatic sketch of dilatable bronchial cannulae. (Van Allen)

The clinical observation that these mechanical factors are not commonly operative in the extra-abdominal group of operations, a group in which a reduced but still substantial incidence of postoperative atelectasis is also seen, led Lindskog in 1941<sup>8</sup> to theorize that histamine-like substances are absorbed from sites of operative or other trauma which by their action of bronchial constriction and hypersecretion set the stage for the secondary action of already recognized and accepted mechanical factors. The latter determine the preponderantly higher incidence in the hernia-laparotomy group of operations.

That histamine-like products of cellular disintegration are absorbed systematically in tissue trauma has been demonstrated by Blalock<sup>9</sup> and by Katzenstein, Mylon and Winternitz.<sup>10</sup> During crush and tourniquet shock, respectively, these writers observed the appearance of a toxic substance in the thoracic duct lymph of dogs. The collected lymph when injected into normal

dogs elicited a histamine-like vasodepressor response in approximately one-half the animals.

To test this theory of a humoral factor in the development of postoperative pulmonary complications, inquiry was made into the effect of chemically pure histamine and certain antihistaminics on collateral respiration in dogs. This paper constitutes a report of the findings.

#### MATERIALS AND METHODS

For each experiment a healthy dog was anesthetized by intravenous injection of sodium pentothal, in dosages of 35 Mg. per Kg. body weight. A mid-

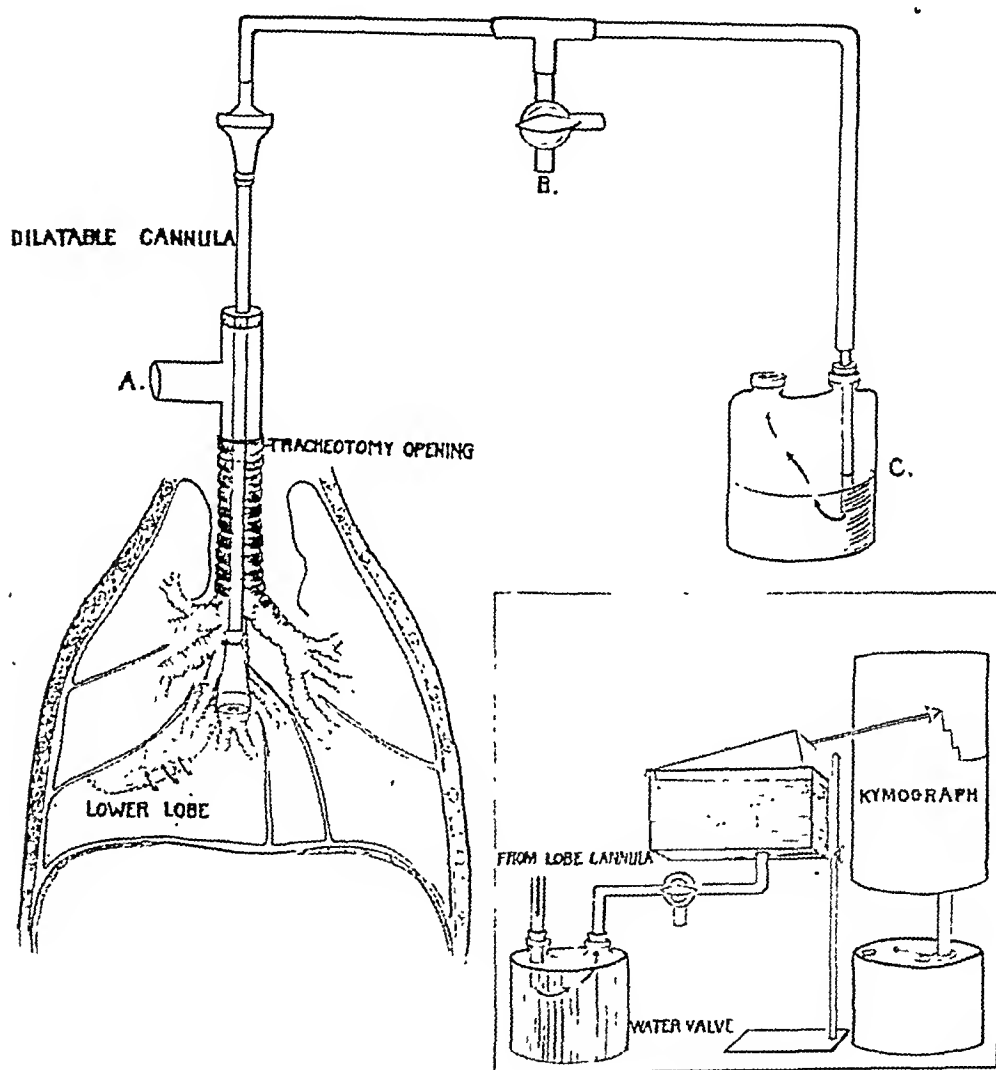
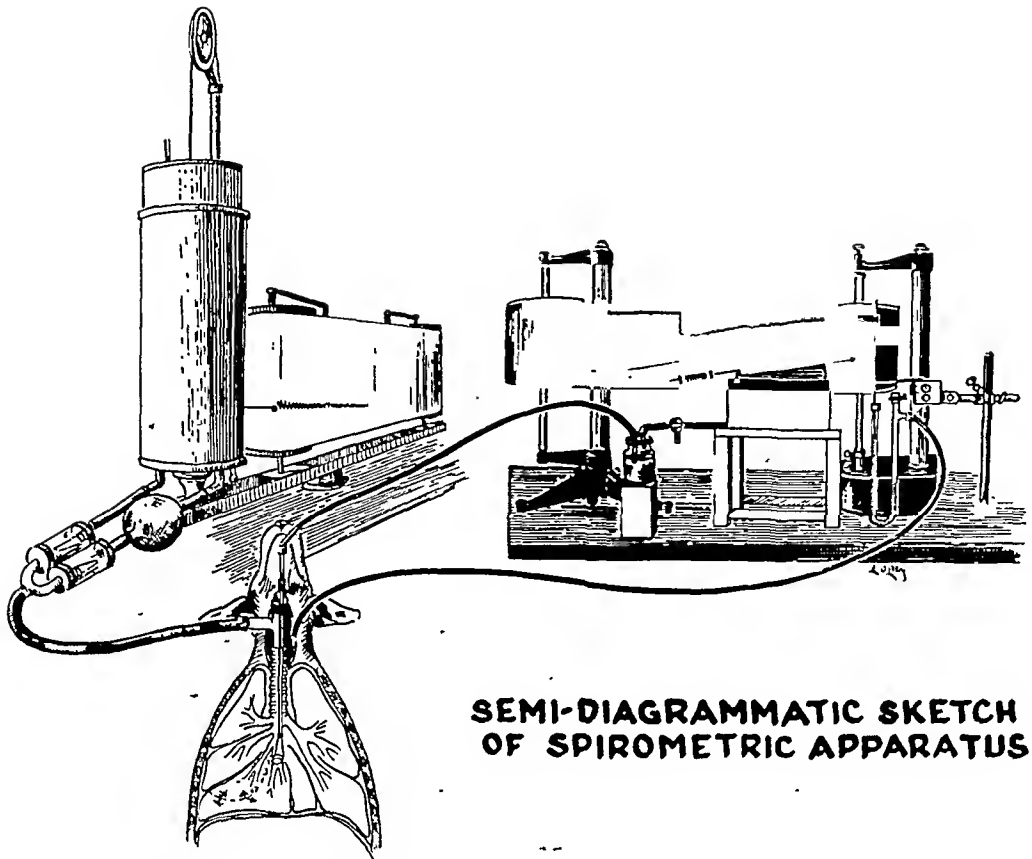


FIG. 3.—Detailed diagrammatic sketch of apparatus used for collection of air from obstructed lung segments. Insert: Arrangement for volume measurements of collaterally transpired air.

line cervical tracheotomy was then performed and a glass cannula was tied securely in the tracheotomy opening. The cannula was of approximately the same caliber as the trachea and had one side arm.

A long slender metal bronchial cannula with a dilatable tip<sup>11</sup> (Fig. 2) was introduced through the tracheal cannula to a point beyond the dorsal segment



**SEMI-DIAGRAMMATIC SKETCH  
OF SPIROMETRIC APPARATUS**

FIG. 4.—Semi-diagrammatic sketch of spirometric apparatus.

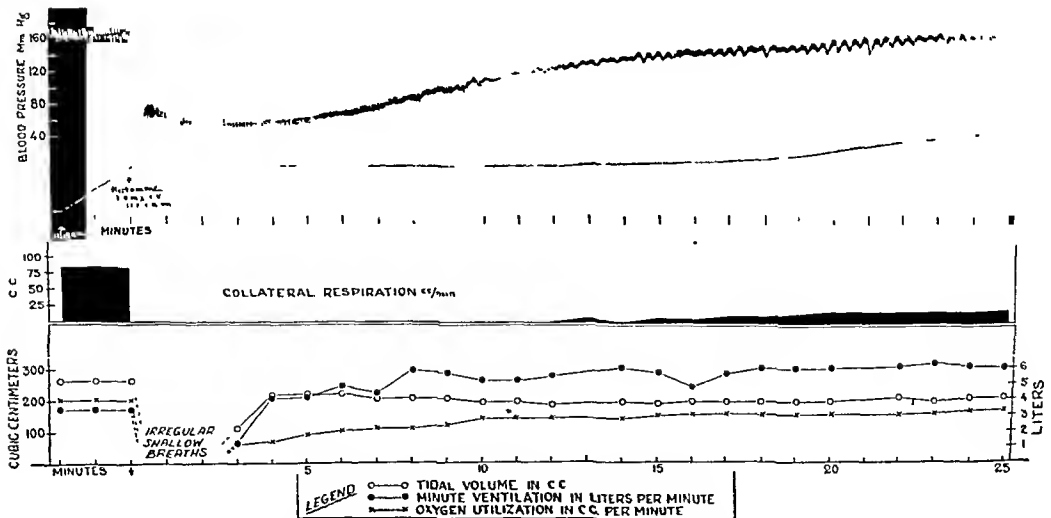


FIG. 5.—Upper: Photograph of actual kymograph record. Administration of 2.0 Mg. histamine causes hypotension, cessation of collateral respiration. Below the record is shown the calculated volume of collateral air in graph form.

Lower: Charted data obtained from large spirometer, showing transient decrease in tidal air and oxygen utilization, with tachypnoea reflected in increased minute ventilation.

bronchus of the right or left lower lobe. The tip was dilated firmly in place. The proximal end of the bronchial cannula was then connected to a delicately balanced and calibrated Krogh spirometer of 450 cc. capacity with a water valve interposed so as to permit expiration only. The rate of collection of the expired collateral air was recorded continuously from the Krogh spirometer on a revolving smoked drum. (Fig. 3.) The tracheal cannula opening through which the bronchial cannula passed was sealed with a rubber cuff and the side-

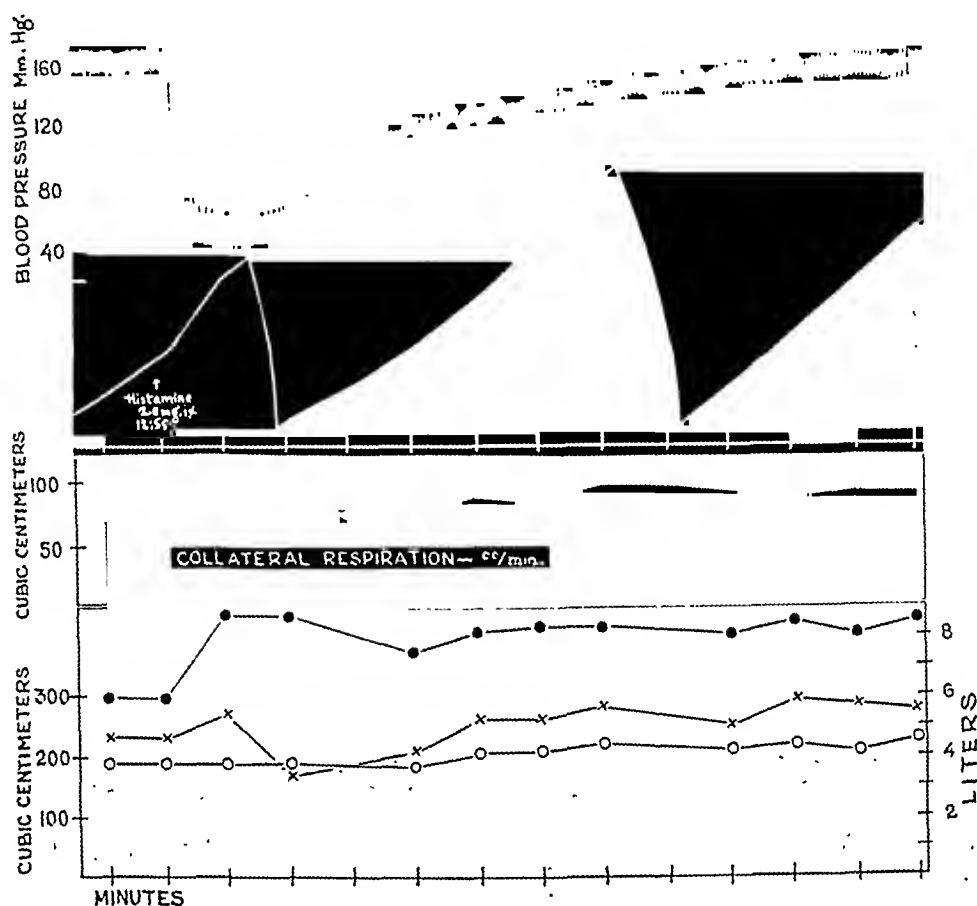


FIG. 6.—Upper: Photograph of kymographic record. Histamine 2.0 Mg. administered 13 minutes following injection of Benadryl 3.0 Mg. per Kg. No interference with collateral respiration, but some actual increase. Downward deflection of curve represents manual emptying of small spirometer.

arm was connected through a CO<sub>2</sub> absorber to a standard Roth-Benedict spirometer containing oxygen. This spirometer recorded on a second kymograph tracing the tidal volume, respiratory rate, and oxygen uptake for the unobstructed portions of the lungs. (Fig. 4.) Simultaneous carotid blood pressure tracing was also recorded.

After each experiment the dog was autopsied to check the position and tightness of the occluding cannula and to rule out the presence of gross pathology.

Six experiments were carried out in which histamine diphosphate was injected intravenously in varying dosages before and after the injection of Benadryl (b-dimethyl amino ethyl benzhydryl ether hydrochloride) and in one

experiment in which Pyribenzamine (N-pyridyl-N-benzy-N-dimethyl ethylene diamine monohydrochloride) was used instead of Benadryl. No effort was made to determine the relative potencies of these antihistaminic agents.

# RESULTS

As in the human, there was a wide range of individual sensitivity to histamine among these dogs. In all instances, however, histamine in doses of 0.02-2.0 Mg. resulted in a marked diminution or elimination of collateral respiration

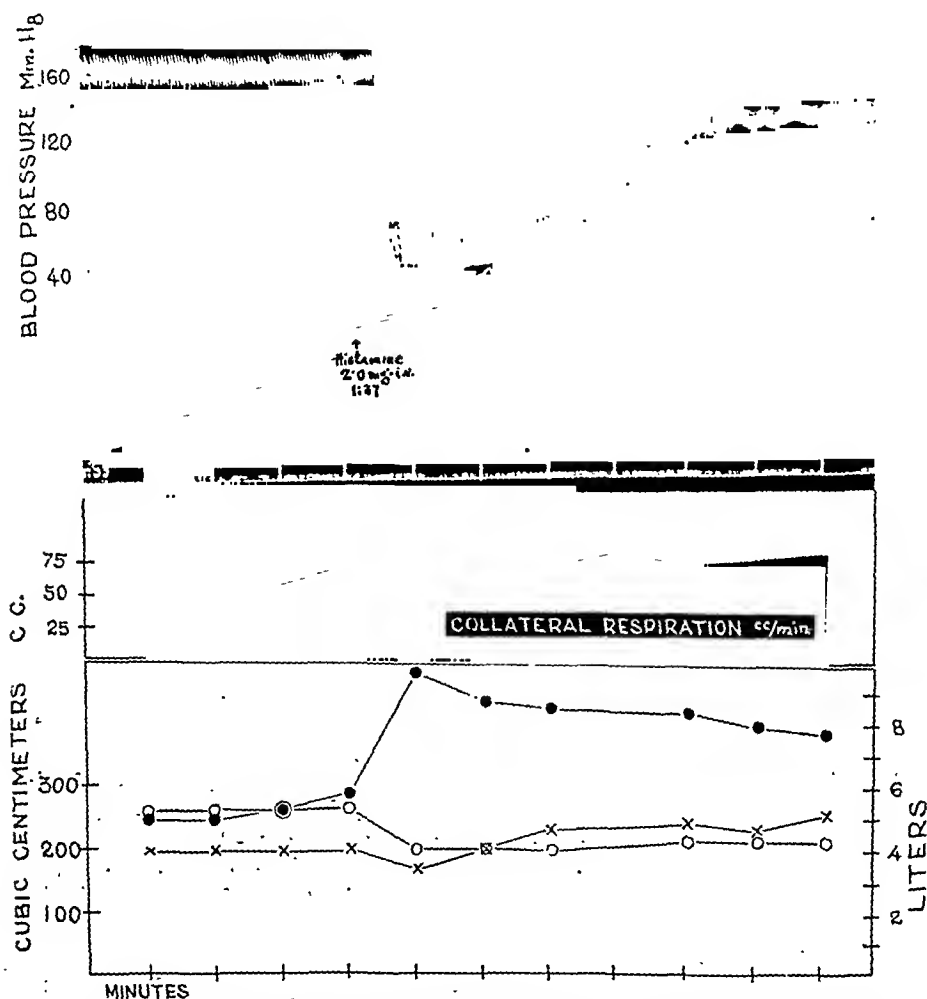


FIG. 7.—Effect of intravenous injection of histamine (2.0 Mg.) one hour following injection of Benadryl 3.0 Mg. per Kg. Note slight interference with collateral respiration.

followed by a gradual return of this function to the preinjection rate in a period of minutes. Associated with this phenomenon were marked tachypnoea, variable decrease in tidal volume, and a striking reduction in oxygen utilization for the whole animal. These were of shorter duration than the depression of collateral respiration. (Fig. 5.) The degree of response was found to be in proportion to the dose. Elimination of collateral respiration for a short period was observed in one animal with doses as small as 10 gamma per kilogram body weight.

# COLLATERAL RESPIRATION

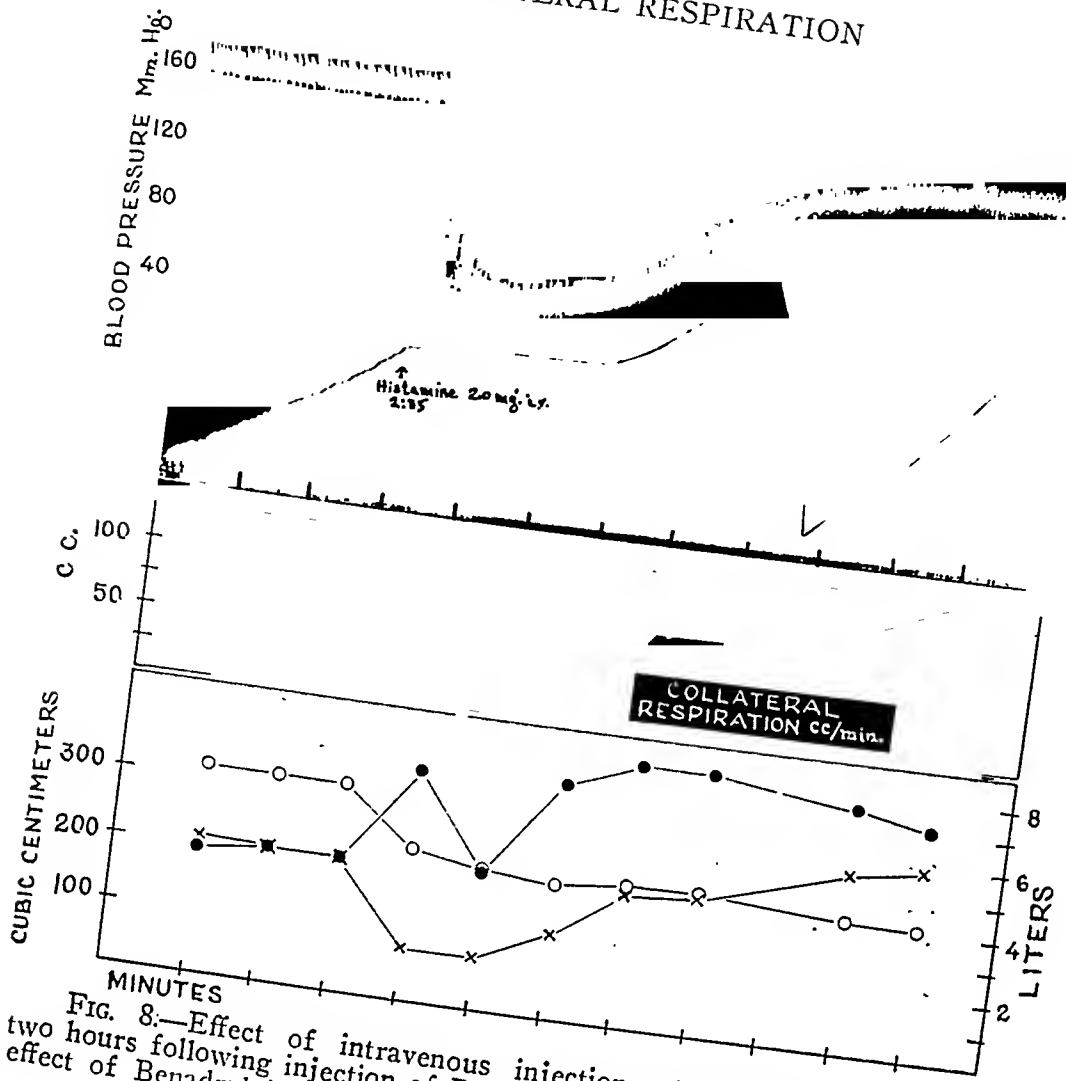


FIG. 8.—Effect of intravenous injection of histamine (2.0 Mg.) two hours following injection of Benadryl 3.0 Mg. per Kg. The protective effect of Benadryl is seen to be decreasing.

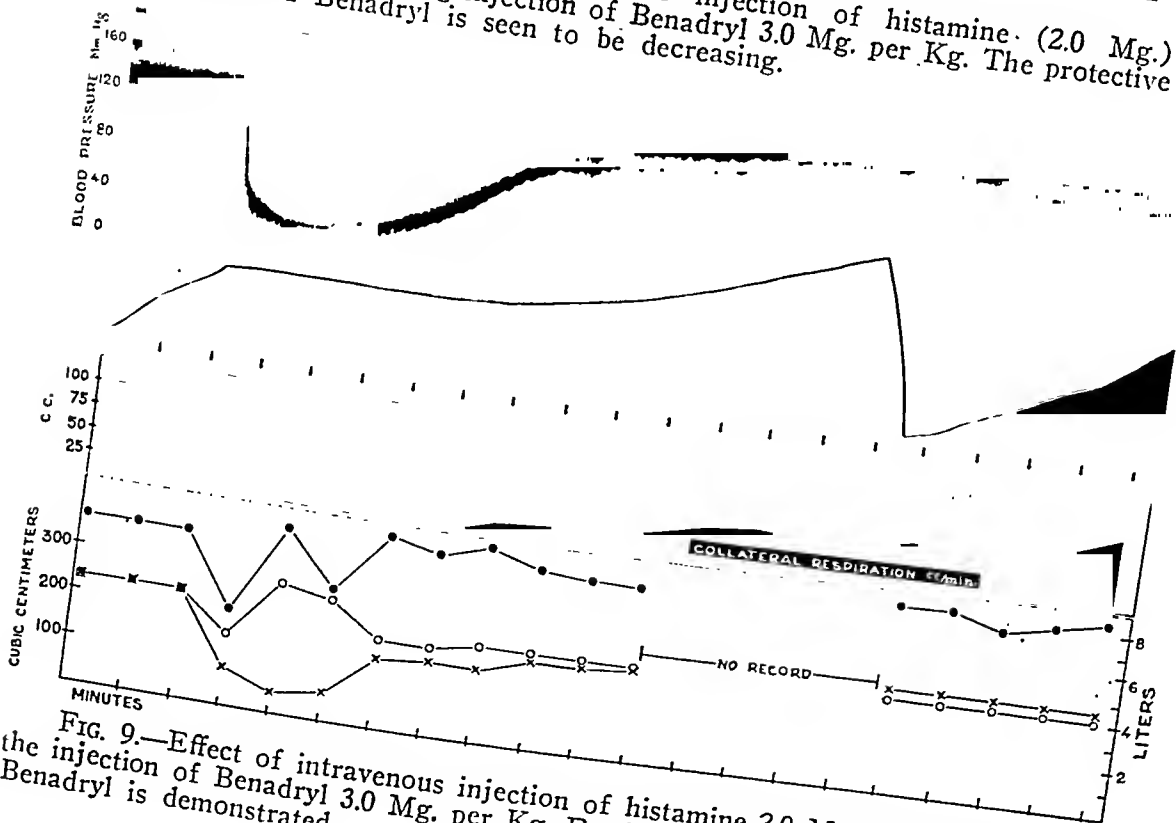


FIG. 9.—Effect of intravenous injection of histamine 2.0 Mg. five hours following the injection of Benadryl 3.0 Mg. per Kg. Further decrease in the protective effect of Benadryl is demonstrated.



Benadryl in doses of 1-3 Mg. per kilo and Pyribenzamine in a dosage of 1 Mg. per kilo given prior to injection of histamine completely eliminated the depressive effect of histamine on collateral respiration. In fact, the tachypnoea which resulted from histamine injection following Benadryl increased the rate of collateral respiration if the interval between injection was only a matter of a few minutes. (Fig. 6.) The protective effect of these agents was maximal for 1-1½ and 3 hours, respectively, and then disappeared gradually over the ensuing five or six hours. (Fig. 7-9). Benadryl was found to protect against single doses of histamine as high as 10 Mg.

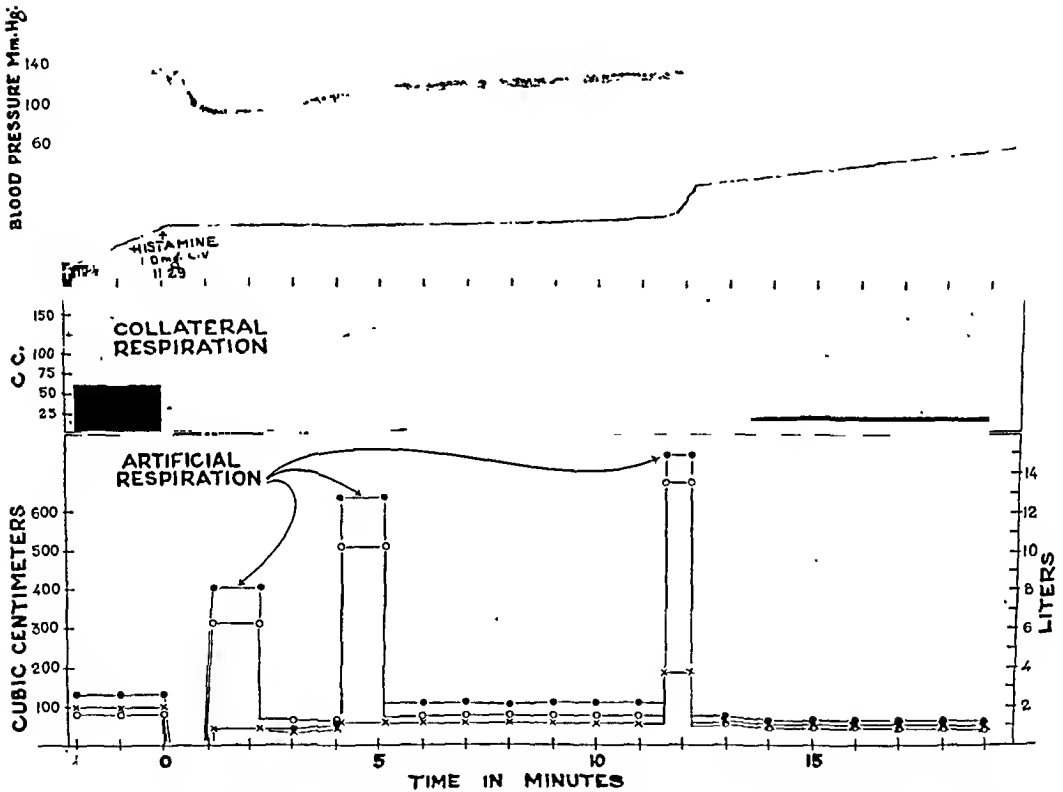


FIG. 10.—Vigorous artificial respiration performed by elevating and depressing the Roth-Benedict spirometer drum had no effect when collateral respiration was totally obstructed by histamine. Following the spontaneous return of this function artificial respiration increased the rate of collateral flow.

*Note:* The tidal volumes recorded during artificial respiration are exaggerated by the rise and fall of water in the spirometer jacket during this manipulation.

To rule out the decrease in tidal volume after histamine as an important factor in the reduction of collateral respiration other experiments were carried out. During the period when collateral respiration was blocked the animal was given forceful artificial respiration by manually elevating and depressing the large spirometer drum. No collateral respiration occurred. Following the spontaneous return of collateral respiration during the recovery period, however, artificial respiration resulted in a marked increase in collateral respiration (Fig. 10.)

Rapid intravenous administration of Benadryl in a dosage of 3 Mg. per kilogram caused a transient but marked fall in blood pressure, followed by a lesser and more prolonged hypertension.<sup>12</sup> Accompanying these vascular effects was a short period of apnoea followed by a decrease in tidal volume and increased respiratory rate lasting for several minutes. During the period of apnoea no collateral respiration occurred and there was a relative decrease in the rate of its production during the period of decreased tidal volume and increased respiratory rate. (Fig. 11.) These effects were not observed when the dose of Benadryl was injected slowly. The same effects, but of more marked degree, were observed following the rapid intravenous injection of Pyribenzamine, 1 Mg. per Kg.

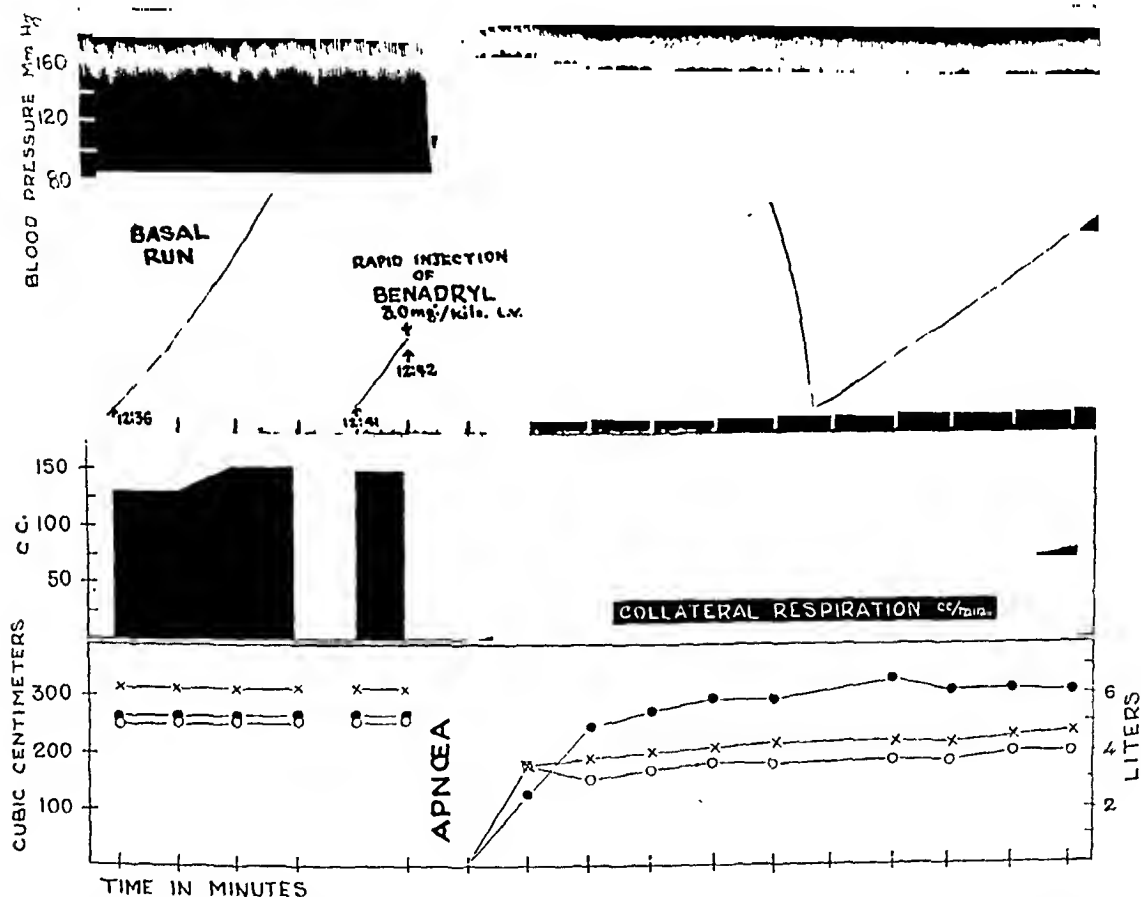


FIG. 11.—Showing the biphasic blood pressure response and decrease in collateral respiration in proportion to reduction in tidal volume following rapid intravenous injection of Benadryl 3.0 Mg. per Kg. No vascular or respiratory response was obtained following the slow intravenous infusion of the same dose.

#### DISCUSSION

The mechanism by which histamine interferes with collateral respiration is still conjectural. The bronchoconstrictor and edema-producing actions of this drug are well recognized. That bronchoconstriction alone is responsible seems unlikely in view of the fact that some oxygen uptake (although reduced) was present during the periods when collateral respiration was altogether absent. Studies with ANTU-induced pulmonary edema in dogs reveals that collateral respiration is eliminated before rales can be heard with the stethoscope.<sup>13</sup>

This suggests that pulmonary edema results in a thickening of the interalveolar membrane of sufficient degree to obliterate the pores of Kohn before sufficient fluid is exuded into the respiratory passages to be clinically evident as rales. That a degree of pulmonary edema may play a role in the collateral respiratory-blocking effect of histamine remains a possibility, but the rapidity of action makes this unlikely.

These observations also have an interesting relation to a side-action of curare, a drug which is now of widespread use as an adjunct in anesthesia. The intravenous injection of curare was shown by Anrep and his co-workers<sup>14</sup> to release histamine from muscle tissue in dogs, which circulated in the blood in physiologically active form. Subsequently, Comroe and Dripps<sup>15</sup> found that intracutaneous and intra-arterial injections of curare in man produced typical histamine-like wheals and flares. These observations were confirmed by Grob, Lilienthal and Harvey<sup>16</sup> who also described evidence of general vasodilatation and increased secretion of gastric juice following intra-arterial injection of curare, and found these to be inhibited by the previous or simultaneous injection of antihistaminic agents. Recently, Landmesser<sup>17</sup> measured the broncho-constrictor action of intravenous curare in dogs and found it to be inhibited by antihistaminics. The release of histamine following administration of curare may explain the reported occasional occurrence during curarization of alarming respiratory difficulty and sudden severe hypotension which resemble the effects of histamine.<sup>18-22</sup>

The effect of histamine on collateral respiration as demonstrated in this study suggests that histamine release by curare presents an additional factor in the production of postoperative pulmonary complications. However, this factor may be outweighed by the beneficial effects of curare, namely, shorter operating time and better exposure with less trauma. Thus far no report of a carefully controlled study of postoperative pulmonary complications following curare in anesthesia has been published.

If histamine-like substances are released by various types of tissue trauma, the facts established by our experiments suggest that the absorption of these substances following operative trauma may act to produce an interference with collateral respiration, thus setting the stage for the development of postoperative pulmonary atelectasis. Furthermore, this mechanism may be inhibited by prior administration of antihistaminics.

#### CONCLUSIONS

1. Histamine when administered to normal dogs in total dose of 0.02-2.0 Mg. causes a temporary abolition of the collateral respiratory function in the lung lobe.

2. This action of histamine is inhibited by prior administration of antihistaminics (Benadryl and Pyribenzamine).

3. The possible relation of these findings to the production of postoperative pulmonary atelectasis and its prevention is discussed.

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DISCUSSION.—DR. GUSTAF E. LINDSKOG, New Haven, Conn.: I think that the experiments themselves are reasonably clear cut. The link in the chain that is missing is evidence that in surgical operations and other types of trauma sufficient histamine is released and absorbed into the blood stream to cause this type of remote effect on the lung. Clinical experience suggests that there is a basic humoral mechanism in the production of early postoperative pulmonary complications. They occur

typically very early, and they occur preponderantly in patients who have had severe operative trauma and prolonged operations. There are two factors that the external or extralaparotomy group of operations and the internal or laparotomy group have in common. These are operative trauma and sedation, and sedation I think plays a very important role. However, the common primary mechanism may be the humoral mechanism, the effects of which we have tried to demonstrate here from the experimental side.

I would like to point out that with this cannulation technic, which was first developed by Dr. Van Allen in 1930, there exists an excellent opportunity for anesthesiologists to study very accurately and quantitatively the effect of certain agents on the peripheral pulmonary and bronchial mechanism.

DR. EDWARD D. CHURCHILL, Boston: Dr. Lindskog and his colleagues have taken up the problem of the point at which histamine or histamine-like substances act on smooth muscle in the lung. It has been known for years that the injection of a small amount of histamine is followed by a sharp rise in the pressure recorded in the pulmonary artery. The smooth muscle of the lung, however, is a very complicated structure. Its distribution varies widely in different mammals. In some species it appears most highly developed in the walls of the arterics; in others, in the bronchial tree. It is difficult to isolate and identify the action of these various components of the smooth muscle structure.

It occurred to us a good many years ago that the sharp rise of pulmonary artery pressure in response to a minute dose of histamine might be a method of biologically detecting the release of histamine from traumatized tissue. At that time the H-substance was in its heyday and everyone was attributing traumatic shock to H-substance. An experiment was set up, using the cat, with a constant recording of the pulmonary artery pressure. An extremity was isolated by a tourniquet and traumatized. The question asked was whether release of the tourniquet, which was found to cause a precipitate drop in systemic pressure, might also produce a rise of pulmonary artery pressure. The assumption was that a wave front of H-substance released from the traumatized extremity would enter the pulmonary circulation and produce a characteristic pharmacologic response. Actually, no detectible rise of pulmonary artery pressure occurred. When a minute dosage of histamine was placed in the venous system of the extremity before loosening the tourniquet, its release was followed by the characteristic effect.

Any conclusion regarding the release of H-substance from traumatized tissues should be clearly earmarked as an assumption. This hypothesis was set up by physiologists during and after World War I, on the basis of poorly controlled experiments and superficial clinical observations. It has taken years to put it in its place as an unproven assumption.

# STUDIES ON THE USE OF POLYTHENE AS A FIBROUS TISSUE STIMULANT\*

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ATTENTION WAS DIRECTED toward the irritating properties of cellophane by Page<sup>2</sup> in 1939, who wrapped the kidney of dogs in cellophane, in order to produce hypertension. Since that time, clinical and laboratory reports have been made showing successful obliteration of aneurysms and complete interruption of large blood vessels as a result of fibrosis secondary to cellophane implants. Concurrently, other reports have been made demonstrating the use of cellophane and cellophane-polythene (polyethylene) because of its physiologically inert characteristics and lack of fibrous tissue stimulating characteristics. In other words, clinical use is being made of an apparently similar or related substance with end results that are diametrically opposed.

Poppe and De Oliveira,<sup>7</sup> in 1946, reported the results of their studies of the comparative characteristics of various types of cellophane. They showed that substances identified as varieties of cellophane caused slight tissue reaction; whereas the substance referred to as polythene\*\* caused a marked fibrous reaction.

Ingraham, in 1947, and in contradistinction to Poppe's findings, reported that polythene film and polythene tubes were implanted into the brains of experimental animals without evidence of gross or histologic tissue reaction. In contrast to the work of Poppe and De Oliveira, he also demonstrated marked tissue reaction to du Pont "Cellophane (PT 300)", a substance which Poppe had found to be comparatively inert.

Personal correspondence with the du Pont Company has elicited the comment that there is apparently some confusion in identity between cellophane and polythene, and that in their experience, this had not been unusual even in commercial application.

Implantation, into human tissue, of foreign substances other than suture material, has been attempted to correct or reinforce tissue defects or to bridge over breaks in tissue continuity. Bone plates, vitallium tubes and lucite balls all represent recent examples of this principle. Such substances are useful because of their physiological inertness and because they produce minimal tissue reaction. Certain varieties of cellophane apparently meet this requisite. Donati,<sup>1</sup> in 1936, demonstrated the inert characteristics of cellophane. Wheeldon,<sup>3</sup> in 1939, reported the use of No. 300 moisture proof transparent cellophane, as a permanent tendon sheath, to prevent adhesions. In 1943, McKeever<sup>6</sup> reported the use of cellophane following synovectomy, as an interposition membrane, to prevent adhesions of two surfaces.

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\* Read before the American Surgical Association, Quebec, Canada, May 28, 1948

\*\* Polythene; cellophane-polythene and polyethylene are synonymous terms.

In September, 1947 at the Clinical Congress of the American College of Surgeons, reports were made by Brown, Gunlay and Craig: "Use of Polythene As A Dural Substitute"; by Gunlay and Gray: "Molded Plastic Tubes: An Experimental Study With Special References To Their Use In Reconstruction Of The Common Duct", and by Hockworth: "Replacement Of The Thoracic Aorta With Polyethylene Tubing: An Experimental Study".

Our interest in the problem has evolved from a search for a substance that will cause a relatively controlled fibrous tissue stimulation, without, at the same time, having the undesirable characteristics of a foreign body. Laboratory and clinical studies have confirmed our impression that "polythene-du Pont" meets these requirements. We prefer the latter terminology in order to clarify the present misunderstanding regarding the characteristics of various types of cellophane and polythene. Disparities noted in results with polythene are apparently not due to variations of the basic chemical formula or the raw product, but upon the method by which it is secondarily converted into film, blocks or tubes. For purposes of clarity, discussion in this paper will be limited to the effects of "polythene-du Pont" as obtained in 1.5 mil film directly from the E. I. du Pont De Nemours and Company Inc. This company prepares polythene film from crude polythene by a "solvent cast" method. The finished product is pure polythene with the exception of less than one percent of dicetyl phosphate, the stripping agent.

Other manufacturers prepare polythene film and polythene tubes, from crude polythene, by means of a "melt extrusion process". This process does not entail the use of antioxidants, stripping agents or plasticizers, the end product being pure polythene.

In attempting to correlate the results of various investigators, this variation in method of manufacturing was noted. The implications, which are obvious, will be discussed under animal experimental implant data.

Inertness and minimal tissue response associated with implantation of foreign substances are essential characteristics, when indicated. Nevertheless, in certain conditions, there is need for a substance for tissue implantation that will stimulate, within reasonable limits, the production of fibrous tissue.

The desirability of occluding aneurysms has been understood since their recognition as a clinical entity. Ideally, the procedure should occlude, or in some way eliminate the aneurysm without jeopardizing the distal circulation. The concept of gradual arterial obliteration was originated late in the 18th century. Various ingenious externally compressing devices were ultimately found to be unsatisfactory, and not without their dangers. Direct attack is frequently limited, both by reason of endangering viability of tissue and by anatomical difficulties. A procedure that will gradually obliterate an aneurysm with absolute certainty, and not entail the use of mechanical devices, or repeated operative procedures, should assure an optimum distal circulation.

Polythene-du Pont falls into the category of a plastic, it being a long-chained polymer of ethylene. As stated previously, this product is pure poly-

thene with the exception of less than one percent of dicetyl phosphate. In medical literature, polythene is usually referred to as polyethylene. When it was found that polythene-du Pont possessed fibrous tissue stimulating qualities, possible carcinogenic excitant characteristics were excluded. The latter observations extended over a period of five months. Polythene-du Pont implants were made into 20 mice, representing two cancer susceptible strains and two cancer resistant strains. Co-carcinogenic agents (Hematoxylin and Croton oil) were also injected. The implantation of polythene-du Pont into mice did not give rise to tumors, or reveal evidence of carcinogenic stimulus.

Fibrous tissue stimulating characteristics of polythene-du Pont were



studied in a series of animal experiments that included dogs, rabbits and guinea pigs. Following its implantation, microscopic and histologic studies were made at intervals of 10 days, and one, two and three months. Paralleling control studies were also made. It was found that polythene-du Pont caused an inflammatory response in tissue, far in excess of that seen in control animals. This inflammatory reaction was characterized by edema, hyperemia, fibroblastic proliferation and lymphocytic and eosinophilic infiltration. Effects on fascia, muscle and peritoneum, as well as blood vessels, were studied. (Fig. 1 & 2.) Implants were sutured in situ, and their location carefully marked.

FIG. 1 (Guinea Pig 10).—Low power photomicrograph of the implantation site of polythene-du Pont, thirty-four days after its introduction into the muscles of the abdominal wall (hematoxylin and eosin). Note the extensive fibrosis. Areas of scarring are composed of fibroblasts, in a loose stroma with young fibrocytes arranged in whorls. Histocytes laden with blood pigment are present.

In addition to these observations, crude polythene flake, polythene film prepared by the "melt extrusion" process, which is pure polythene, as well as dicetyl phosphate were implanted into the tissues of experimental animals. The

results of these observations are shown in Fig. 3, 4 and 5.

Based on these observations, we believe that pure polythene is comparatively inert when implanted into tissue, and does not cause a fibrous tissue reaction. Polythene film prepared by the "stripping process" of the du Pont Company is adulterated by dicetyl phosphate. Apparently the tissue excitant



factor noted in polythene-du Pont is dicetyl phosphate with polythene simply acting as an inert media of transmission.

The effects of polythene-du Pont on a diffuse dilatation of the common carotid artery and on a fusiform aneurysm of the abdominal aorta are illustrative of the clinical application of the principle of treatment by fibrosis.

#### CASE REPORTS

Case 1.—M. E. W. (History 35073), a 66-year-old white female admitted to the University Hospital with a complaint of "hoarseness" associated with a "lump" in the right side of the neck. Three years previous to admission, she noticed difficulty in singing, and an increasing hoarseness. There were no complaints of cough, palpitation, dyspnea or syncope.

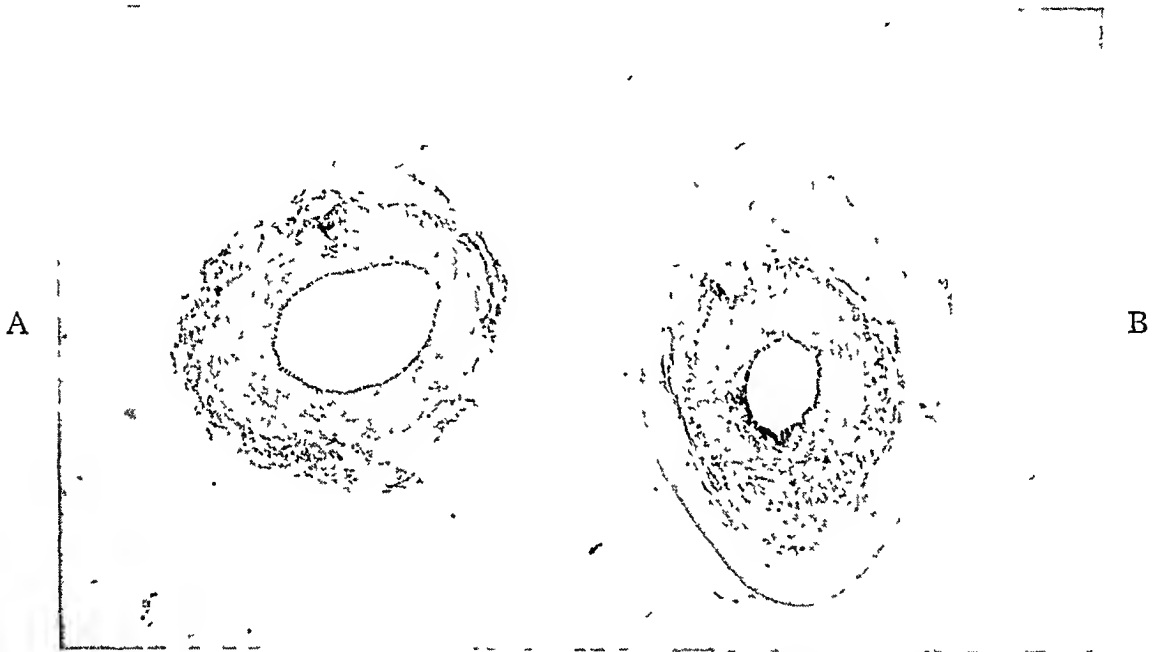


FIG. 2 (Dog 11).—Low power photomicrograph. A—Normal carotid artery. B—Carotid artery thirty-eight days after implantation of polythene-du Pont. Note the substantial constriction. The adventitia and periadventitia is thickened with dense collagenous connective tissue. Focal lymphocytic infiltration is present. The media is free of significant scarring.

A pulsating mass, synchronous with the heart beat, just above the right sternoclavicular area was noted. It measured approximately 5 cm by 3 cm. No thrill or bruit were present. The radial pulses were equal and synchronous; the heart slightly enlarged, to the left. Serology negative. Roentgen examination:—Moderate cardiac hypertrophy; aorta tortuous but not dilated; no soft tissue mass seen in the lower cervical region.

Under endotracheal cyclopropane anesthesia, the right cervical area was explored. The right subclavian artery was sclerotic and tortuous. The right common carotid artery was tortuous and markedly dilated, simulating a fusiform aneurysm. The innominate artery was also sclerotic and dilated. The common carotid was mobilized and the internal jugular vein and vagus nerve, as well as the recurrent laryngeal nerve, were isolated. A single layer of 1.5 mil polythene-du Pont was overlaid about the common carotid artery, and tacked in place with interrupted double zero plain catgut sutures. The bifurcation of the innominate was overlaid in a similar manner. The incision was closed without drainage.

The postoperative course was essentially without event. The patient returned to work at the end of four weeks, after operation. Examination at the end of four months, revealed no evidence of hoarseness, and no history of recurrence of hoarseness. The mass in the right side of the neck had disappeared. Pulsations in the right carotid region, were within normal limits.

Case 2.—G. F. (History 36376), (Fig. 6), a 64-year-old white male, admitted to the University Hospital with a complaint of a "throbbing lump" in the left lower abdomen, and weakness of the left lower extremity with cramping. The "weakness and cramping" were noticed about one year prior to admission to the hospital. Fol-



FIG. 3 (Rabbit 4).—Low power photomicrograph of implantation site of crude polythene flake 15 days after its introduction into the muscles of the abdominal wall (hematoxylin and eosin). Defects that are seen represent polythene deposits. Infiltration of lymphocytes and polymorphonuclears is characteristic of a foreign body reaction.

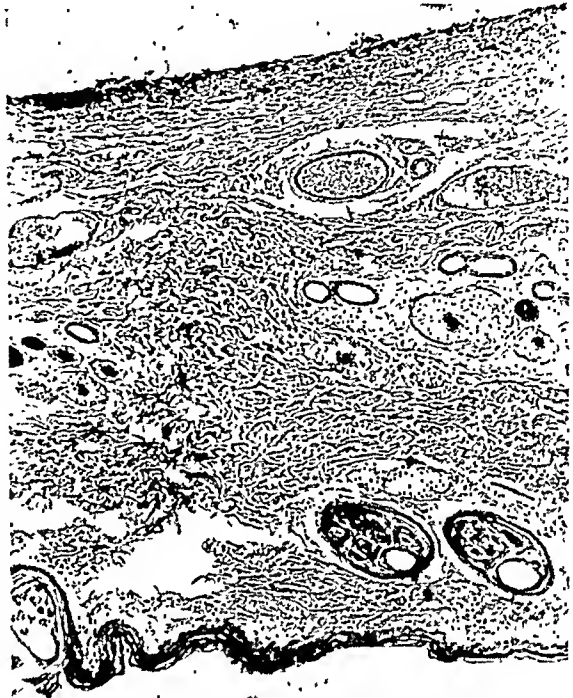


FIG. 4 (Dog 22).—Low power photomicrograph of implantation site of pure polythene film ("melt extrusion process") 12 days after its introduction into the subcutaneous plane of the abdominal wall (hematoxylin and eosin). Note the narrow margin of scarring and tissue reaction along the site of polythene implant. Giant cell and lymphocytic infiltration is minimal.

lowing development of the leg symptoms, a hard mass was noted in the left side of the abdomen, that gradually increased in size.

*Physical examination*:—Evidence of generalized arteriosclerosis, with an expansile, pulsating mass about  $3\frac{1}{2}$ " by 4", to the left of the abdominal midline, nonadherent to the abdominal wall. Blood pressure in the right leg was 130/70; it could not be obtained on the left. Peripheral vessels, including the femoral, could not be palpated on the left side; all vessels were easily palpated on the right. The left foot was cool and ischaemic. Pulsations in the abdominal mass were synchronous with the heart beat. Neurological and Serology examinations were negative. E. K. G.:—Myocardial abnormality and possible coronary disease. Roentgen examination:—Aortic arch calcified; extensive calcification of the abdominal aorta with marked enlargement, the left

lateral border extending about 5 cm. lateral to the lumbar vertebra; calcification noted from L 2 to the lumbosacral joint. Definite bony erosion not seen. The colon, by means of barium enema, filled readily with no filling defects and no displacement.

Under spinal pontocain anesthesia, an abdominal exploration was performed through a long left muscle splitting incision. A fusiform aneurysm of the abdominal aorta was found that extended from the level of the first lumbar vertebra, to its bifurcation into the common iliacs. The jejunum, at its point of fixation by the ligament of Treitz, was displaced forward, and was adherent to the aneurysm. The peritoneum was reflected from the aneurysm, and the aneurysmal sac exposed over about 80 percent of its surface. The right common iliac appeared to be normal in character. The left common iliac was distorted and compressed by an overlying bulge in the aneurysmal sac; very feeble pulsations were obtained in this vessel. The vena cava was visualized. No attempt was made to mobilize the posterior aspect of the aneurysm, overlying the vertebra.



FIG. 5 (Rabbit 3).—Low power photomicrograph of implantation site of dicetyl phosphate 13 days after its introduction into the muscles of the abdominal wall (hematoxylin and eosin). Note the fibrosis and lymphocytic infiltration. Foreign body giant cells are scattered throughout the section, with young fibrocytes arranged in whorls.

It was noted that experimental animals with large fascial and muscle defects fibrosed without evidence of herniation following polythene-du Pont implants, whereas these defects persisted in control animals. (Fig. 7.)

In general, foreign substances retard rather than aid the normal process of wound repair. Jenkins,<sup>10</sup> in 1947, in his studies with gelfoam sponges, stated "fibroplasia develops rapidly under the sponge, and in addition, invades the interstices of the sponge. This offers a lattice work for the growth

Single strips of 1.5 mil polythene-du Pont were tacked over the exposed areas of the aneurysm by means of fine silk sutures. Cellophane was overlaid along the medial margins of the exposed aneurysmal sac, in order to afford protection to the vena cava. The reflected peritoneum was then approximated by means of interrupted silk sutures. The abdominal incision was closed without drainage.

The postoperative course was essentially without event. Examination two months postoperatively revealed that the patient had returned to his occupation as a watchman. The abdominal mass, by palpitation, had decreased in size about two-thirds. The subjective sensation of "throbbing" had disappeared. He was completely free of pain. Particularly noteworthy, was the fact that pulsations were obtained in all of the peripheral arteries of the left lower extremity, as well as the right, and that both feet were warm.

#### IMPLANTATION OF POLYTHENE-DU PONT INTO THE ABDOMINAL WALL

The end effects of polythene-du Pont are apparently due to fibrosis.

of fibroblasts, thus giving reinforcement and structural support”.

More recently, Koontz<sup>11</sup> has studied the effects of tantalum mesh in the repair of ventral hernias. He has shown that when tantalum mesh is implanted into tissue defects, the mesh becomes covered by a very thick, tough envelope of fibrous tissue.



FIG. 6 (G. F. 36376).—Aneurysm of the abdominal aorta, secondary in arteriosclerosis, extending from L 1 to its bifurcation into the common iliacs. Peritoneum reflected from aneurysmal sac, and polythene-du Pont being plicated onto its wall.

Experimental studies were not made to determine the possible merits or advantages of these substances. It was thought that the type of fibrous tissue reaction noted with polythene-du Pont might be both desirable and advan-

tageous in the problem of recurring hernias, particularly in those associated with large fascial defects. This principle has been applied clinically in 15 instances, the following of which is a typical example.

#### CASE REPORT

**Case 1.**—J. M. G. (History 36335), (Fig 8) a 50-year-old white male, admitted to the University Hospital with a complaint of bilateral recurrent inguinal hernia. Bilateral inguinal hernioplasties had been performed 15 years and 3 years respectively, prior to the present admission. During a six to seven months period previous to this admission, it had been noticed that the hernia on the right side "bulged into the scrotum."

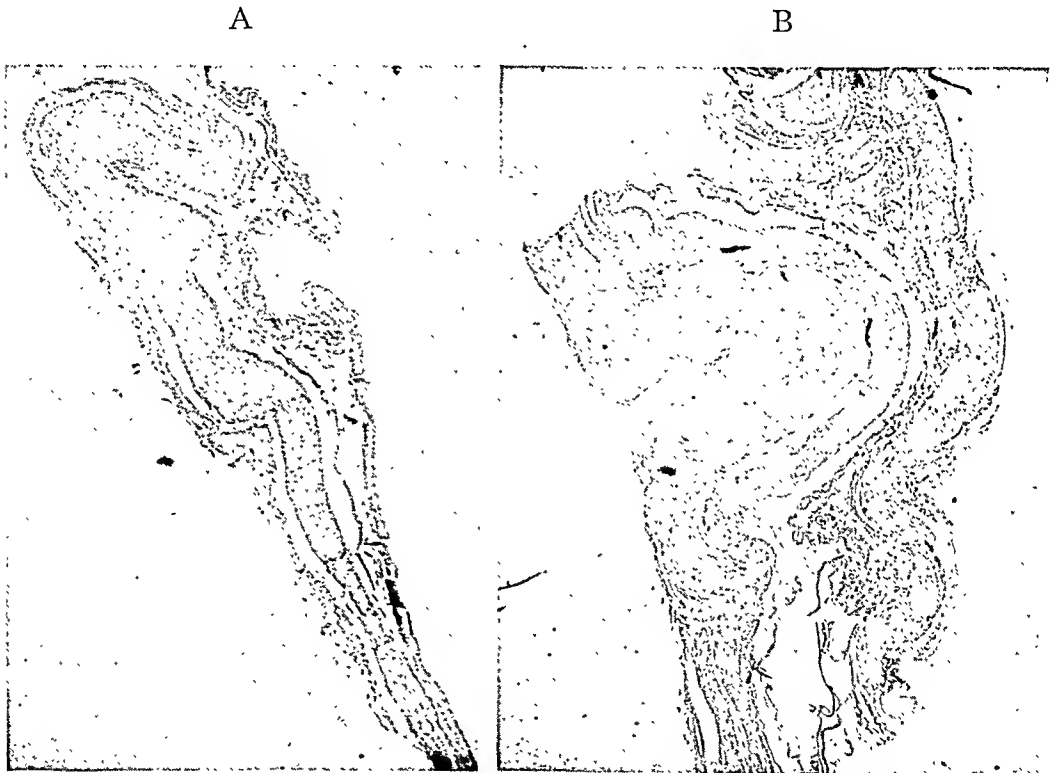


FIG. 7 ("a"—Dog 19; "b"—Dog 20). Low power photomicrographs showing "a"—control cross section of anterior abdominal wall 54 days after rectus muscle and anterior rectus sheath had been removed. "b"—same procedure 54 days after implantation of 1.5 mil polythene-du Pont into defect. Note greater fibroblastic proliferation and scarring in "b" as compared to "a".

Physical examination was essentially negative except for a complete irreducible inguinal hernia on the right, and an incomplete reducible inguinal hernia on the left.

Under spinal pontocain anesthesia, bilateral inguinal hernioplasties of the Halstead type were performed. The right side entailed considerable difficulty in identifying anatomical planes. The sac on this side, which was densely adherent, extended into the scrotum, and contained incarcerated omentum, which was resected. Following ligation of the peritoneal sacs on their respective sides, a single strip of 1.5 mil polythene-du Pont was tacked over the neck of each sac. Another strip was placed between the peritoneum and the site of approximation of the conjoined tendon, to Poupart's ligament. This strip extended from slightly above the internal ring to the pubis. An additional strip of 1.5 mil polythene-du Pont was placed anterior to these approxi-

mated structures, and beneath the fascia of the external oblique muscle. The incision was then closed without drainage. The conjoined tendon in this patient was thin and transparent. The fascia of the external oblique muscle was a poorly defined structure. Except for a superficial infection, the patient's convalescence was comparatively without event. At the end of ten days, the incisional areas were brawny and indurated. This brawniness and induration persisted for about six weeks. Follow-up examination at the end of five months, did not reveal any suggestion of recurrence.

#### COMMENT

Polythene-du Pont implants have now been used in eleven inguinal hernias and in four of the ventral type. In each instance, the problem either

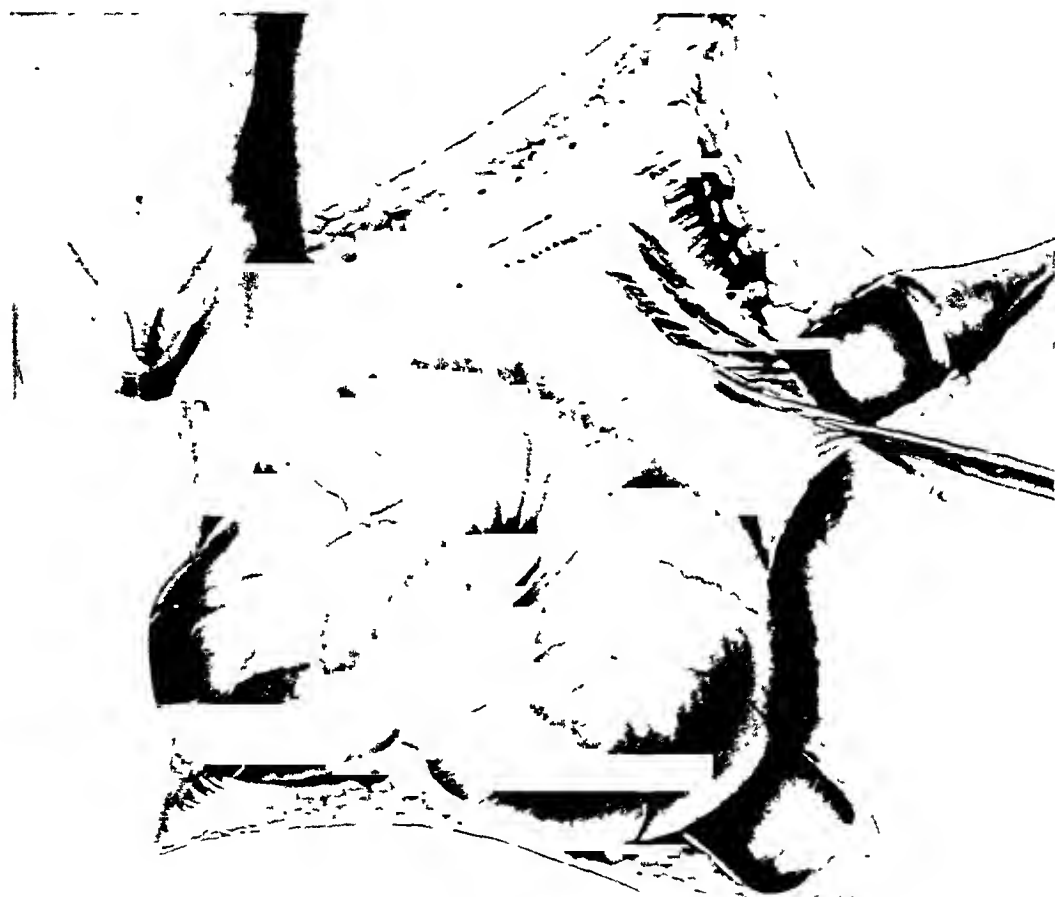


FIG. 8 (J. M. G. 36335).—Third recurrence, bilateral inguinal hernias, showing size of sac on right side which contained incarcerated omentum.

of repeated recurrences, or large fascial defects was presented. With the exception of the case reported above, none of the operative procedures were associated with secondary infection or unusual complications. The series is too small, and the period of postoperative observation too short, to establish a true evaluation of the effectiveness of this procedure. There has been no evidence of recurrences. The longest postoperative period of observance in this series is eight months; the shortest three months.

#### DISCUSSION

Polythene-du Pont, because of its fibrous tissue excitant characteristics, was utilized in the treatment of aneurysms and recurrent hernias. In retro-

spect, it appears that the same result could have been accomplished by the direct use of dicetyl phosphate, the chemical adulterant appearing in this type of polythene. Dicetyl phosphate, when implanted into the tissues of experimental animals, causes a prompt and violent type of fibrous tissue response. A supplemental report will attempt to demonstrate its late effects on tissue, as well as principles involving its utilization.

Some absorbable substance may ultimately prove to be a more satisfactory medium for application. If dicetyl phosphate can be combined with a substance such as gelfoam, the results should be more advantageous.

#### CONCLUSION

1. The principle of tissue fibrosis offers a method of obliterating aneurysms. It presents the advantages of gradual obliteration, with optimum development of collateral circulation. It has the disadvantages of not being directly controllable.

2. The principle of fibrous tissue stimulation may offer a field of usefulness in the problem of fascial defects and recurring hernias.

3. Polythene-du Pont represents a method of accomplishing a relatively controlled type of fibrous tissue reaction.

4. The type of reaction noted with polythene-du Pont seems to be due to dicetyl phosphate and not to polythene.

5. Pure polythene implants are well tolerated by tissues and are associated with a minimal tissue response.

6. Conflicting results regarding the use of polythene in aneurysms, patent ductus arteriosus, and obliterative procedures are probably due to variances in method of manufacturing the film.

7. Implantation of polythene-du Pont when fibrous tissue reaction is not indicated would be most undesirable.

8. Clinical use of cellophane, polythene or any other plastic, carries with it the urgent requirement of knowledge of both the chemical and physical characteristics of the product being used.

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DISCUSSION.—DR. HILGER P. JENKINS, Chicago: Dr. Yeager has drawn to our attention that a manufacturer uses an irritating substance such as diacetyl phosphate in the fabrication of the finished product, which makes a very striking difference in the behavior of this material in the tissues. This brings up the question of asking the Council on Pharmacy and Chemistry of the American Medical Association to co-operate with the surgical profession by maintaining a comprehensive file on new commercial materials which may be of value in surgery, so that those who are pioneering with these new products may have the benefit of information which may not be made available to individuals by manufacturers, unless one is as persistent as Dr. Yeager has been.

DR. HERMAN E. PEARSE, Rochester, N. Y.: I know of no subject on which there is so much confusion as in the physiologic response to plastics. There are four papers that can be used as an illustration. Poppe and Yeager have pointed out the irritant properties of polythene; Ingraham and Clagett have used polythene to prevent irritation.

Some years ago I reported on the occlusion of great vessels by wrapping them with cellophane. Later I carried out another group of experiments and could not repeat my original results. Experiments were undertaken to determine why this occurred. They were predicated on three hypotheses: One, that there was an individual sensitivity of the animal, and this has not been proven or disproven. Second, that the cellophane itself was impure and some contaminant in it caused the irritation. That has been demonstrated here, and I certainly congratulate Dr. Yeager. However, I do not believe that this can be the only irritating substance, for many possible contaminants are used in the manufacture. The third possibility is that the cellophane itself may be irritating and there is a coating on it that protects it from the tissue. This thought was suggested by the fact that if you soak it for a long time, or if you use various methods of sterilization, your results will differ. The greatest activity is obtained when the substance is boiled.

We have compared 300 P T cellophane from Dupont, 300 P U T from Dupont, polythene from Dupont, polythene from the manufacturer who supplied Ingraham, a number of cellulose products provided me, and to date the more I work in this field the more confused I become. The results are erratic.

I wish to conclude with one thought. If one uses these substances to produce irritation and they do not do so, you have not obtained your objective but you have done no harm. Should one use them to avoid irritation and have them cause irritation, I agree with Dr. Yeager, that the results will be catastrophic.

DR. DANIEL C. ELKIN, Emory University, Ga.: We have employed polythene in conjunction with a partial occlusion of the aorta by a metallic band, in order to bring about a subsequent complete occlusion as a result of the fibroblastic cellular response to this material. The early experience, particularly that of Halsted, showed that the use of a metallic band alone frequently resulted in ischemia of the vessel wall



with subsequent rupture. The use of polythene or of some other irritating variety of cellophane, as advocated by Pearse, at times brought about a complete obliteration of the vessel but failed to produce uniformly a complete occlusion. We, therefore, combined the two methods, using a cuff of polythene about the aorta of the experimental animal, and over this placing a metallic band of tantalum so compressed as to produce about 50 per cent occlusion. It is believed that the fibrosis produced by the polythene serves to protect the vessel from erosion of its wall by the metallic band. Microscopically, it is readily seen that a heavy buffer of fibrous tissue is produced at the margin of the band and extends along the course of the artery as a bulkhead against erosion and aneurysmal formation. The vessel beneath the band continues to atrophy, but the entire area is encased in a sheath of fibrous tissue. Thus, the use of the two materials overcome the inherent disadvantages of either material alone, and the period of time required for complete occlusion of the artery is greatly decreased.

DR. AMOS R. KOONTZ, Baltimore: Dr. Yeager has certainly put his finger on one thing that is much needed in surgery; that is, something to increase fibrous tissue in various places. There is one place in which I have been trying to find something that will increase fibrous tissue; namely, in reinforcing suture lines, especially in hernia repair. I have tried various agents experimentally, such as gelfoam and fibrin foam, without very startling results, hoping to find something to cut down the use of some of those noxious agents our President spoke about yesterday.

The reports I have seen in the literature by Ingraham and others who have used polythene to repair dural defects state that it is inert, causes no irritation and no increase in fibrous tissue. The irritating type of polythene, which Dr. Yeager has used and which causes an increase in fibrous tissue, should be of great value in reinforcing suture lines when weak structures are sutured together. In a great many cases, especially in hernia repair, there are no available tissues surrounding the defect with which to strengthen the suture line. The possibilities of the irritating type of polythene in these cases are well worth considering.

I am going to have the temerity to speak of one of the agents that Dr. Gallie condemned yesterday; that is, tantalum mesh. I have tried this experimentally in dogs, resecting the rectus muscles on each side and replacing them with tantalum mesh sutured to the fascia around the edges of the defect, and leaving nothing but the tantalum mesh between the subcutaneous tissue and the peritoneum. It is remarkable to note, several months later, the amount of fibrous reaction that develops. The fibrous tissues grow through the mesh, all around the mesh, and it becomes covered with a very heavy layer of fibrous tissue and gives a strikingly firm abdominal wall. Whether the tantalum mesh stimulates fibrous tissue to grow, I do not know; but I have in mind some experiments to try to find out whether this is the case or whether the tantalum simply acts as an inert framework to support the growths of fibrous tissue. I have used it in a good many cases of large ventral hernia, in which the defect couldn't be closed and where there were no tissues to be mobilized to close the defect; or, if tissues were available, they were too weak to be of value. Of course, you can undercut, you can make flaps, you can make relaxation incisions; but even then the tissues are very weak in many cases, and if you haven't something strong to close the defect with, you will not get a cure.

I operated on one woman, using tantalum mesh, who measured 60 inches in her stocking feet and weighed 256 pounds in her nightgown, and the fat was actually oozing through all her fascial tissues everywhere. I do not think she could be cured without putting in some extraneous material. Maybe polythene will do the trick in these cases. When I saw Dr. Yeager's paper on the program, I already had some polythene to try out; and I am going to try it because if it will do the same thing for ventral hernias that tantalum mesh will do, it is possible it might be more desirable.

# PROTHROMBIN ACTIVITY\*

## A Diagnostic Test for Early Postoperative Venous Thrombosis

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THE PREVENTION OF POSTOPERATIVE VENOUS thrombosis and pulmonary embolism has received a great deal of attention during the past few years. Sufficient clinical data have been accumulated to establish definitely that modern prophylactic methods can materially reduce the incidence of postoperative thrombo-embolism. This decreased incidence is due primarily to the use of proximal vein ligation and/or anticoagulants, but recent improvements in pre- and postoperative care have also played a definite role. Allen and associates<sup>1</sup> have been the foremost advocates of vein interruption. Heparin has been used most extensively in Sweden<sup>2</sup> and dicumarol has been favored in this country by Barker<sup>3</sup> and others. Each of these methods, or combination of methods, has its firm advocates but experience has shown that any one of the three can be effective when properly used. (Table I)

These methods present serious problems. Routine prophylactic bilateral vein ligation entails an added operating room procedure. Many surgeons view with alarm large scale normal vein ligation, and there is reason to believe that edema of the legs and other complications occur in some individuals as a result. Routine prophylactic postoperative anticoagulants require very careful laboratory control if they are to be both safe and effective. This is especially true with dicumarol, as the dosage must be individualized for each patient and plasma prothrombin activity must be determined daily during the treatment. This is a major technical and economic problem for the well equipped hospital and an insurmountable problem in the hospital with inadequate laboratory facilities. If the problem of thrombosis is approached statistically, only about 6% of postoperative patients require prophylaxis, but there has been no proven method by which this relatively small group can be distinguished from those patients who will not have thrombosis. Our recent experience indicates that the prothrombin activity of the plasma in the postoperative period may serve as a helpful test in predicting those patients who are liable to thrombo-embolic complications.

Our first efforts to find a laboratory test which might be of value in detecting early thrombosis were stimulated by the work of Waugh and Ruddick.<sup>4</sup> They used a heparin dilution method of determining blood coagulation time and found the time was decreased during bed rest, in

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acute inflammatory conditions, in the presence of hemorrhage, and during the postoperative period. Using this method we have found marked reduction in coagulation time in several postoperative patients who developed thrombosis. Increased whole plasma prothrombin activity was also noted in those patients who developed thrombosis. The determination of the prothrombin activity of plasma is a simple laboratory procedure, and it seemed worthwhile to study its alterations in the postoperative patient.

There are conflicting reports in the literature concerning the relation of prothrombin activity to thrombosis. Tuft and Rosenfield<sup>5</sup> concluded from their studies using dilute plasma that an acceleration of prothrombin time is not suggestive evidence of a tendency to thrombo-embolism. Hurn, Barker and Mann<sup>6</sup> found that the levels of antithrombin and prothrombin are often outside observed normals in patients having a tendency to thrombosis, but that high and low values are present in about equal numbers. Levy and Conroy<sup>7</sup> found decreased prothrombin times during ether anesthesia with a return to normal within 24 hours after operation. They used the bedside

TABLE I.—*Prophylactic Treatment of Thrombo-Embolism*  
*Comparison of Vein Ligation and Anticoagulants*

Treatment	Number Patients	Thrombosis and Embolism	Fatal Embolism	Authors
None .....	302	11%	2.9%	Craaford & Jorpes
Heparin .....	352	0	0	
None .....	832‡	3.9%	0.7% (6 cases)	Edgar Allen et al.
Dicumarol .....	832	0.4% (3 cases)	0	
None .....	458*	12%	5.7%	Arthur Allen
Vein ligation .....	458	1.1% (5 cases)	1 case	

‡ Estimated Complications—Abdominal Hysterectomy.

\* Selected Cases—Older Age Group.

method of determining prothrombin time. The work of Bancroft and Stanley-Brown<sup>8</sup> gives support to the thought that prothrombin activity may give a clue to thrombosis. They determined the "clotting index" according to the formula—C.I. equals  $\frac{\text{Prothrombin}}{\text{Antithrombin} + \text{Fibrinogen}}$ . An index of 1.0 or

over indicated a tendency to thrombosis and one of 0.3 or less, a tendency to bleed. In a series of postoperative patients, 65% had a normal clotting index and an uneventful convalescence. Thirty-five per cent had a high index and although no frank signs of phlebitis developed, this group all had fever and a prolonged convalescence without any demonstrable cause. Patients with phlebitis all had high indices as did seven patients with pulmonary emboli. They studied patients preoperatively and on the seventh and ninth postoperative days, and believed that a high index indicated a tendency to thrombosis. Shapiro<sup>9</sup> found hyper-prothrombinemia in patients who had venous thrombosis or a pulmonary embolus. He determined prothrombin time on diluted (12.5%) plasma as well as on whole plasma and found the most consistent decrease in the dilute plasma. His results using whole plasma were variable and at times he found increased prothrombin times when

thrombosis was actually present. He concluded that a decreased prothrombin time found with dilute plasma was an aid in the differential diagnosis of thrombosis. The data which are being presented indicate that an increase in the prothrombin activity of whole plasma precedes the appearance of clinical thrombosis although at the time when thrombosis is evident, the prothrombin activity may be normal or less than normal.

#### METHODS

The plasma prothrombin activity has been studied in two series of post-operative patients. In the first series of 73 patients, prothrombin activity was determined just before and within 6 hours after the operation, also daily until the sixth postoperative day. Patients selected for study were those in the older age group who were undergoing major surgery and those who had a previous history of phlebitis. All blood samples were drawn and the determinations were done by one of us (R. S.). In the second series the blood samples were drawn by the members of the surgical house staff or medical student externes on the first and second or third postoperative days. The determinations of prothrombin activity were done by one of three experienced technicians under close supervision. The method used for determining prothrombin activity is as follows, and is essentially that described by Quick.<sup>10</sup>

1. *Preparation of thromboplastin.* A fresh human brain is stripped of vessels, gross blood is washed off with normal saline, and the tissue macerated by beating at medium speed in an electric mixer. Water and lipids are extracted with large volumes of acetone at low temperature; usually four changes of acetone are required. The granular mass is filtered and then placed in a vacuum desiccator, and the acetone removed by an oil suction pump. The dry powder is kept in a desiccator under refrigeration. For use, 0.3 Gm. of the dry powder is suspended in 10 cc. normal saline and the mixture digested at 50-55° C. for 20 minutes with frequent shaking. It is then centrifuged at 1500 r.p.m. for five minutes and the turbid supernatant fluid pipetted off. This is mixed with an equal volume of .024 M calcium chloride solution and the mixture placed in a water bath at 37° C. just prior to use.

2. *Standardization of thromboplastin.* (Aggeler.<sup>11</sup>) Determinations are run in quadruplicate on two fresh plasma samples from each of five normal individuals. Prothrombin times of whole plasma and dilutions of 60%, 40%, 25%, 20%, 15%, 10% and 5% are determined and a curve constructed from the average values. Prothrombin activity of an unknown is calculated from this curve.

Different individuals may obtain dissimilar results because of differences in reaction time, so they must run checks against each other or carry out separate thromboplastin standardizations.

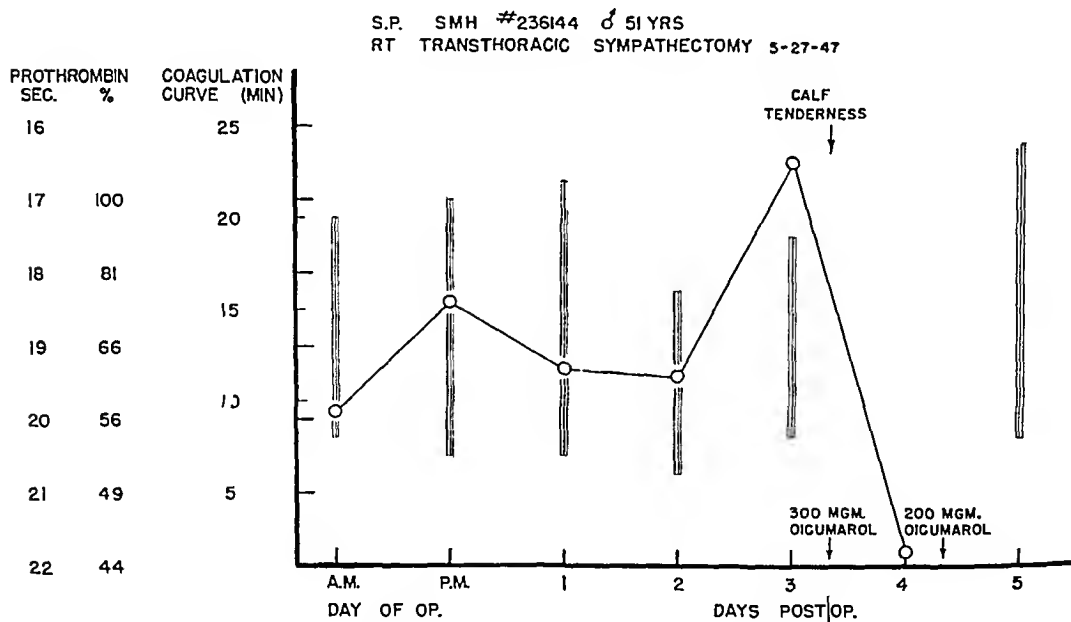
3. *Sampling.* Blood is drawn in a dry syringe, avoiding hemostasis as much as possible, and transferred to bottles containing dry oxalate mixture

(.006 Gm. ammonium oxalate and .004 Gm. potassium oxalate in 5 cc. blood). Hemolyzed or partially clotted blood is not used.

4. *Determination of prothrombin activity.* Blood is centrifuged at 2000 r.p.m. for 10 minutes and the plasma pipetted off. Determinations are run on whole plasma and on plasma diluted to 25% (1:3) with normal saline. 0.1 cc. plasma is pipetted onto a clean watch glass which is placed in the water bath at 37° C. To this is added 0.2 cc. of the thromboplastin-calcium chloride mixture; at this moment the stop watch is started. The mixture is stirred constantly with a glass rod; the end point is reached when clot formation is first observed. A black background facilitates observation of the end point. Determinations are run in triplicate.

## OBSERVATIONS

The coagulation time in 20 postoperative patients was studied using the heparin-dilution method of Waugh and Ruddick.<sup>4</sup> Two of these patients

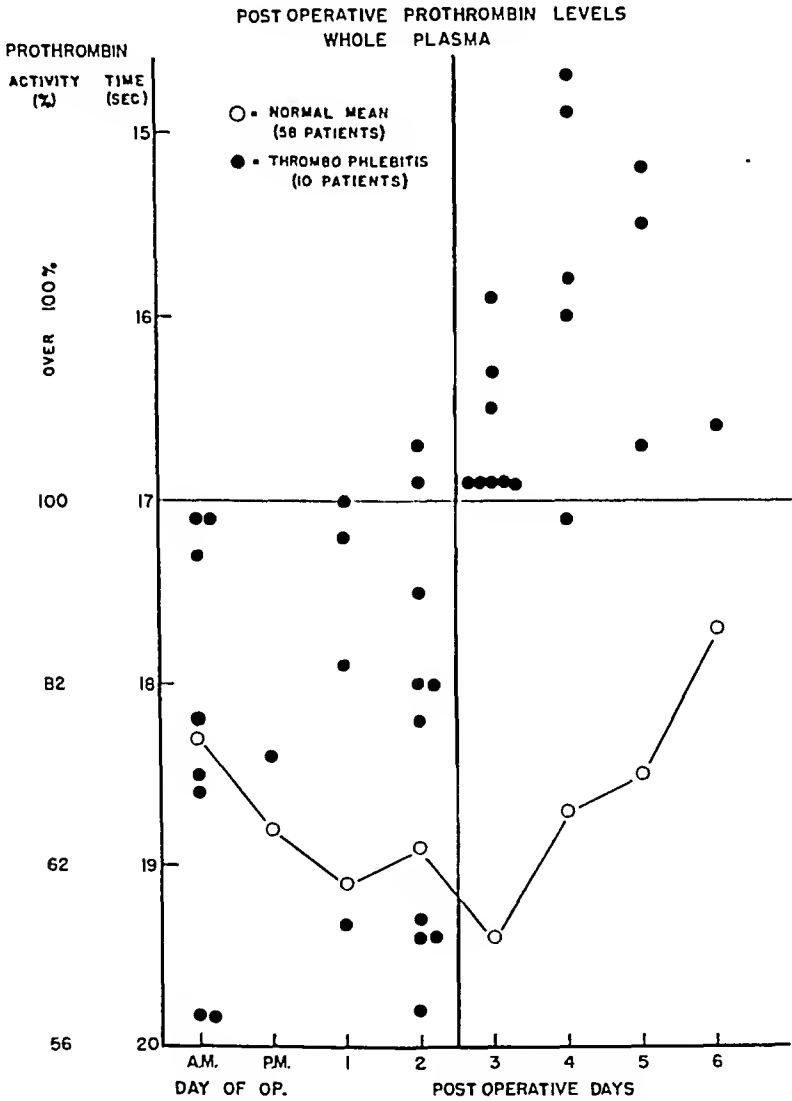


GRAPH 1.—Hypercoagulability in postoperative period, with concomitant rise in whole plasma prothrombin activity and subsequent thrombosis.

showed a decrease in coagulation time prior to the onset of clinically recognizable thrombosis; however, the procedure requires 15 cc. of blood, takes 30 minutes or more to complete, and the end point is difficult to standardize. At the same time, prothrombin activity of whole plasma was being determined in these patients, and Graph I shows the results in one which influenced us to concentrate on the study of prothrombin. This patient had a transthoracic sympathectomy for hypertension, and on his second and third postoperative days, the coagulation time was decreased. On his third postoperative day the prothrombin activity increased to over 100%, and late in

the afternoon minimal calf tenderness was noted. The following day the diagnosis of thrombosis of the leg veins was definite and he was treated with dicumarol.

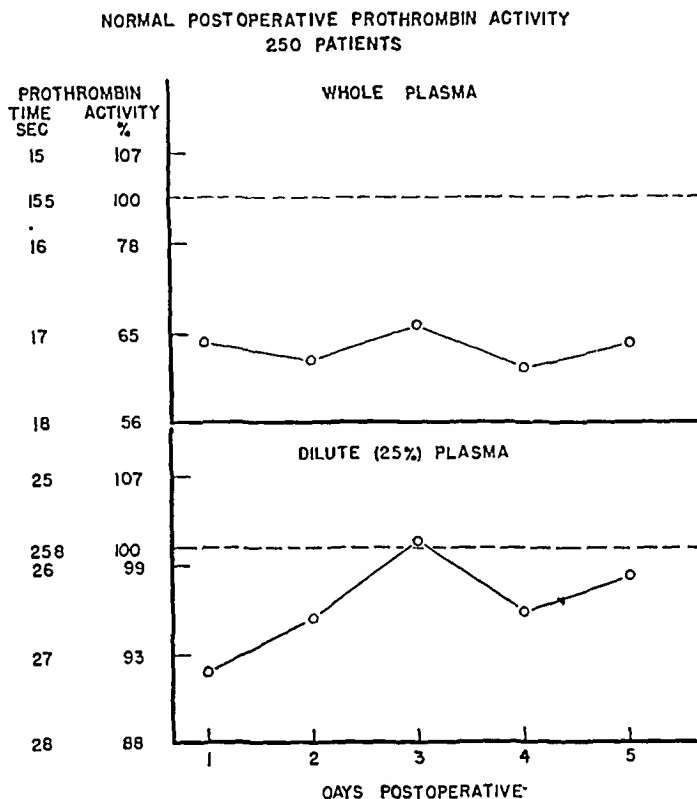
Graph II indicates the results obtained in the first series of 73 patients. Fifty-eight of the patients had no evidence of thrombosis during their post-operative course; the means of prothrombin activity of whole plasma are shown. (Graph II). There is a tendency for prothrombin activity to decrease



GRAPH II.—Hyperprothrombinemia in 10 patients who subsequently developed venous thrombosis. Black dots represent single prothrombin determinations. The remaining 5 patients in this series who showed hyperprothrombinemia received prophylactic dicumarol.

until the third postoperative day with a return to preoperative levels usually by the sixth day. This return to preoperative levels occurs sooner in young individuals. Ten of the first 73 patients studied developed definite venous thrombosis as a postoperative complication. Their prothrombin levels are indicated by the black dots (Graph II). There was nothing significant noted

preoperatively or on the first postoperative day, but two patients had levels above 100% on the second day, and all were above 100% by the third day. None of these ten patients had signs of thrombosis on the second or third days, but all developed definite signs within the next three days. Five of these patients were treated with dicumarol and five were not. In some of



GRAPH III.—Mean normal prothrombin activity in 250 patients (second series).

the untreated patients, the prothrombin level remained high after the third day, but the levels may be normal or even below normal when thrombosis is clinically evident. The remaining five patients received prophylactic dicumarol because of hyper-prothrombinemia.

Postoperative prothrombin activity has now been studied in 382 surgical patients. The levels in patients who do not develop thrombosis correspond very closely with the results obtained in the first smaller series. The prothrombin activity of the *whole plasma* during the first five postoperative days has averaged 61 to 66 per cent (17.4 sec. to 16.9 sec.—15.5 sec. considered 100%)\* (Graph III and Tables I and II). The prothrombin activity of *dilute plasma* varies between 92 and 101% during this same period. The mean values obtained and statistical analysis of these values are presented

\* New thromboplastin of slightly greater potency was used for the determinations in the second series.

in Tables I and II. For statistical purposes, the levels on patients with hyper-prothrombinemia without clinical evidence of thrombosis are included with the control group. This tends to increase the coefficients of variation but these are still well within the probable limits of error of the method.

A summary of the 382 cases is outlined in Table III. There were 73 in the first series, and 309 in the second series. Three hundred and six

TABLE II.—*Postoperative Prothrombin Levels*  
58 Normal Patients

	No. of Patients		Mean		Standard Deviation		Coeff. of Variation	
	100%	25%	100%	25%	100%	25%	100%	25%
Preop. (A.M.) .....	56	50	18.3	32.2	1.25	2.82	.07	.08
Postop. (P.M.) .....	20	13	19.0	36.7	1.78	2.31	.09	.06
Post-op. I. ....	27	21	19.1	35.4	1.27	3.94	.07	.11
Postop. II. ....	32	26	18.9	33.7	1.31	2.58	.07	.08
Postop. III. ....	17	12	19.4	33.3	1.31	2.20	.07	.07
Postop. IV. ....	24	19	18.7	32.0	1.27	2.43	.07	.08
Postop. V. ....	15	12	18.5	33.9	1.79	3.46	.10	.10
Postop. VI. ....	8	7	17.7	31.5	1.71	2.27	.10	.08

Whole Plasma 17.0 sec. = 100% activity.  
Dilute Plasma 29.2 sec. = 100% activity.

patients or 80.1% did not have postoperative hyper-thrombinemia and did not develop thrombo-embolic complications. Sixteen patients developed thrombosis; all had hyper-prothrombinemia prior to the onset of clinical evidence of thrombosis. *No patient in this series who had been studied on the first and second or third postoperative days developed thrombosis without having had preceding hyper-prothrombinemia.*

TABLE III.

	Number	Mean Seconds	Standard Deviation	Coefficient of Variation
1st Day				
Whole Plasma .....	209	17.1	1.42	.083
25% Plasma .....	213	27.2	2.72	.10
2nd Day				
Whole Plasma .....	55	17.3	1.483	.086
25% Plasma .....	56	26.6	3.02	.114
3rd Day				
Whole Plasma .....	133	16.9	1.20	.071
25% Plasma .....	135	25.7	2.30	.089
4th Day				
Whole Plasma .....	45	17.4	1.48	.085
25% Plasma .....	45	26.5	3.16	.119
5th Day				
Whole Plasma .....	23	17.1	1.18	.069
25% Plasma .....	23	26.1	3.10	.119

Whole Plasma 15.5 sec = 100% activity.  
Dilute Plasma 25.8 sec. = 100% activity.

Prophylactic dicumarol was administered to 41 patients in the series. Eighteen patients were started on the drug immediately after the operation because of a previous history of phlebitis or because of marked obesity or other factors which predispose to thrombosis. Twenty-three patients received prophylactic dicumarol beginning on the third postoperative day because of a sudden rise in prothrombin activity (whole plasma) on that day. We would have preferred to treat fewer of these patients in order to obtain



a more accurate evaluation of the test, but the various members of the surgical service were so convinced of the significance of the hyperprothrombinemia that they were unwilling to allow their patients to go untreated. One of these 23 patients received inadequate dicumarol therapy and had a non-fatal pulmonary embolus on the 11th postoperative day. None of the remaining 40 patients treated with dicumarol had any thrombo-embolic complication.

Nineteen patients who had a positive test on the third postoperative day did not develop definitely recognizable clinical evidence of postoperative thrombosis, and this group is worthy of careful analysis. There were 16

TABLE IV.—*Incidence of Postoperative Hyper-Prothrombinemia and Thrombosis*

	First Series No.	Series %	Second Series No.	Series %	No.	Total %
Total Cases .....	73	100	309	100	382	100
Controls .....	56	76.7	250	80.9	306	80.1
Thrombosis (Total) .....	10	13.7	6	1.9	16	4.2
With hyper-prothrombinemia .....	10	13.7	6	1.9	16	4.2
Without hyper-prothrombinemia .....	0	0	0	0	0	0
Prophylactic Dicumarol (Total) .....	5	6.9	36	11.7	41	10.7
With hyper-prothrombinemia .....	5	6.9	18	5.8	23	6.0
Without hyper-prothrombinemia .....	0	0	18	5.8	18	5.7
Hyper-prothrombinemia Without thrombosis .....	2	2.7	17	5.5	19	5.0

males and 3 females. Seventeen patients of the 19 were out of bed on the first postoperative day, were made to walk and were not allowed to sit in a chair. The other two were made to exercise their legs. Ten of the nineteen had unexplained tachycardia and fever during the postoperative period, but because frank evidence of thrombosis did not develop, they are included in this group. It is probable that they had thrombosis, as many clinicians believe that unexplained tachycardia and fever are signs of venous thrombosis, and are adequate reason for vein ligation or anti-coagulant therapy. It is noteworthy that five of these 19 patients had surgery performed under tourniquets. Infection is known to cause hyperprothrombinemia and was present in two cases—one had lymphangitis with periphlebitis and the other had peritonitis.

Ten patients in the control group of 306 came to autopsy; none had pulmonary emboli. During this same period, there were five other patients on the surgical service who died with emboli; four were the massive fatal type. None of these patients had been studied, as three had extensive metastatic carcinoma and the other two had surgery performed months before death.

#### DISCUSSION

The first series of 73 patients, which has been discussed in detail elsewhere,<sup>12</sup> was small and carefully controlled. Patients selected were those undergoing major abdominal or thoracic surgery, especially those with marked obesity or a history of previous thrombo-embolic disorders. It was

felt that if this test were to be of any value in the prediction of thromboembolism, it must be applicable to large numbers of patients under routine conditions. Therefore, a second series was studied comprising 309 unselected cases operated on between December 1, 1947 and March 31, 1948. Blood samples were drawn by the various house officers, subject to considerable variation in technique and time of day as regards meals, parenteral fluid administration, etc. Major surgical procedures of many types were included. Determinations were performed in a routine manner by one of three individuals accustomed to the procedure. As might be expected from the type of cases selected, the incidence of thrombosis in the first series was much higher than in the second; and the over-all incidence appears higher than is actually the case in this hospital because of the exclusion from both series of patients undergoing so-called minor procedures. The lower incidence of thrombosis in the second series is believed due to two factors: a wider selection of cases, and an increasing use of prophylactic dicumarol. In neither series did any patient on whom prothrombin levels were determined develop thrombosis without showing increased whole plasma prothrombin activity prior to the onset of symptoms.

The results obtained up to the present time indicate that the stage is set for postoperative thrombosis on the second or third postoperative days. This tendency to thrombosis can be detected by an *increased prothrombin activity of the whole plasma*. The prothrombin activity of dilute plasma shows greater variation and does not reflect the same characteristic change as is noted in the whole plasma. The determination of prothrombin activity on dilute plasma is generally considered the more accurate method by workers in this field, so it is possible that the change noted in whole plasma is due to some factor in the clotting mechanism other than prothrombin. Further investigation will be required to settle this point. The hyperprothrombinemia which has been found in patients who develop thrombosis occurs before the diagnosis can be made by clinical examination and is present early in the postoperative period (second or third postoperative day). When thrombosis has become definitely established, the prothrombin activity may be normal or even diminished. It is possible that the hyperprothrombinemia reflects beginning thrombosis in the small veins of the foot or calf or about the operative site. It has been present in patients who later developed either superficial or deep thrombosis.

The data presented are not sufficient to permit sweeping conclusions, nor do we believe that the test is 100% accurate in all surgical patients. No patient has been studied who developed thrombosis without preceeding hyperprothrombinemia, but not all patients who had a positive test developed clinical evidence of thrombosis. It is possible that many of this latter group did have thrombosis which was not clinically detectable or that the tendency to thrombosis suggested by increased prothrombin activity was overcome by early mobilization, active leg exercises, and other preventive measures. The

hyperprothrombinemia in patients who had tourniquets used in surgery of the extremities is of interest, and this feature is now being studied.

At the present time we feel that all patients showing hyperprothrombinemia on the second or third postoperative day are candidates for thrombosis, and unless there are definite contraindications, these patients receive prophylactic dicumarol without any other modification of the postoperative routine. It does not seem necessary to reduce the prothrombin to dangerously low levels when dicumarol is being used prophylactically. Heparin is used in the treatment of definite thrombosis until an adequate dicumarol effect is obtained. Vein ligation has not been used in this series of patients, but hyperprothrombinemia might be considered as an indication for ligation by advocates of this method of therapy. Our experience with this test is limited to patients who are not confined to bed for long periods following surgery. No data have yet been obtained on patients immobilized for long periods in traction.

#### CONCLUSIONS

1. A definite increase in prothrombin activity of whole plasma on the second or third postoperative day appears to be a warning of impending venous thrombosis.

- 2 Postoperative hyperprothrombinemia is a valuable test in determining which patients should receive prophylactic measures against thrombosis.

3. Administration of dicumarol when the hyperprothrombinemia develops is effective prophylaxis against thrombo-embolic complications.

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- <sup>12</sup> Mahoney, E. B. and R. S. Sandrock: The Early Recognition of Post-operative Venous Thrombosis. To be published.

DISCUSSION.—DR. FREDERIC W. BANCROFT, New York: I am intensely interested in the work Dr. Mahoney has done, because since 1928 I have been interested in the problem. Dr. Stanley-Brown and I, as many of you know, had worked out a clotting index. In our original series we had about 1600 routine examinations of pre- and postoperative patients, in which we took the values preoperative, five days postoperative and nine days postoperative. We should have made this five-day examination earlier, as Dr. Mahoney has shown. We early dropped from our list the antithrombin, which we felt was of no importance. We did prothrombin and fibrinogen determinations during the latter part almost entirely depending on the prothrombin test. It was not as accurate as that which Armand Quick developed for us at the Fifth Avenue Hospital.

In our series we have had no accidents in those that did not have a high prothrombin content. We did have something similar to what Dr. Mahoney stated; a certain percentage that had high prothrombin times but did not develop external signs of thrombosis. However, in reviewing the charts we would universally find that they ran a higher postoperative temperature than the average case. No one in the low prothrombin group developed accidents. We had at that time the opportunity to examine a lot of patients throughout New York city who had embolic accidents, and all had high prothrombin after the accident with the exception of one case; that was an amputation of the breast, and there was definitely thrombosis of the bacillary vein and emboli in the lungs. I feel that if we can develop first, an idea of the type of patient that is going to develop thrombosis, and give that patient prophylactic therapy, we will do much better than if we ligate a lot of veins or if we overdose a lot of people with dicumarol or heparin, who probably don't need it, and which raises the patient's expense. If we can analyze our cases, or get our danger gauges, if only a few hours before the first physical signs appear, I think we will have made a great step forward, and I want to thank Dr. Mahoney for his excellent paper.

DR. WALTER D. WISE, Baltimore: At a meeting of the Southern Surgical Association in 1946, the statement was made that at Mercy Hospital, Baltimore, we had introduced the prophylactic use of dicumarol in postoperative cases, and that in a rather large series we had had a reduced incidence of thrombo-embolic cases and no deaths. This preliminary report was made with hesitation for fear it would be considered not quite within the realm of fact. We now wish to quote larger figures over a longer period of time and feel more secure in doing so, after noting such statements as those of Barker and his group, the paper today and many other recent articles. Dicumerol has been used in our work because it can be used orally, is easier to regulate than heparin, and is far less expensive. Of course when a quick change is needed we use heparin. The prophylaxis program in actual practice includes various types of surgery, but for purposes of presentation and discussion the category where predisposition to thrombo-embolic complications is most likely, in major pelvic and abdominal surgery, or combinations, has been selected. The number for the period 1944-47 inclusive seems sufficiently significant for comparison and formulation of tentative conclusions. It must be said, however, that larger numbers are most desirable, as well as a longer period of time before definite conclusions can be drawn

For the four-year period, 1944-45-46-47, there was a total of 5335 major abdomino-pelvic operations; 2330 cases were untreated, that is, they were not tested nor treated, with 25 thrombo-embolic complications, 9 embolic phenomena and 6 deaths from pulmonary embolism. There were 3304 cases treated prophylactically with dicumarol, with four thrombotic complications, one pulmonary infarction and one death, probably not actually due to pulmonary embolism. This patient had carcinomatosis with extensive involvement of the liver. She died after being in a comatose state for five days. There were no clinical symptoms of pulmonary embolism, but one was found at autopsy. She did not have dicumarol for about a week.

# ENDOTHELIOMA OF BONE

(Ewing's Sarcoma)

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## INTRODUCTION

There exists a specific type of malignant bone tumor, now designated as Endothelioma or Ewing's sarcoma, which has justified its consideration as a disease entity by reason of its characteristic age incidence, clinical course, therapeutic response, prognosis and the accumulation of a reasonable number of acceptable cases. While the opinion of pathologists may be divided concerning the exact nature or origin of this lesion there now seems to be general agreement as to its distinct cytological features.

By earlier pathologists this tumor was undoubtedly classified with the heterogeneous and inclusive category "round cell sarcoma". In 1866 Lucke<sup>50</sup> first described a primary bone tumor resembling endothelioma. Other reports followed and, in America, Howard & Crile<sup>39</sup> reported 23 cases in 1905, four of which had been personally observed. Ewing revived interest in the condition in 1921<sup>23</sup> and did much to enhance our knowledge of it and to establish it as an important clinical entity.<sup>24</sup>

## GENERAL DESCRIPTION

Though a relatively rare disease, Ewing's sarcoma occurs more frequently than any other primary malignant bone tumor except osteogenic sarcoma. It is an affection of childhood and adolescence with males afflicted twice as often as females. Arising in the medullary or subcortical portion of both long and flat bones and characterized by destruction rather than by production of bone, it later forms bulky swellings of the soft parts overlying the area of involved bone which often assumes a fusiform shape.

Pain is predominately the first symptom of the onset of the disease and disability follows early and progresses proportionately. The onset is often insidious and early symptoms and signs may simulate a pyogenic infection of bone. Progress of the disease is quite variable, being very rapid in some cases while in others a fatal termination may be long deferred. The disease tends to metastasize not only to the lungs as in osteogenic sarcoma, but also to other bones, particularly the skull.

The tumor shows marked radiosensitivity which may be a delusion for, while the early response to roentgen-rays may be most encouraging, the later complications of local recurrence and metastases are most discouraging fea-

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\* Read before the American Surgical Association, Quebec, Canada, May 28, 1948.

tures. The end results, expressed in terms of 5-year recoveries, are extremely poor.

#### MEMORIAL HOSPITAL SERIES

Because of the paucity of published information concerning this tumor, it seems desirable to report the experience of the Bone Tumor Service of Memorial Hospital. During the thirty-year period from 1918 through 1947, there have been admitted to this clinic 179 patients with a tentative diagnosis of Ewing's sarcoma. Some of this group were so classified on the basis of clinical findings alone and others on the basis of clinical and roentgenographic findings only. These have been excluded from our analysis along with some cases with tissue specimens for histologic study in which the original opinion has not been sustained but changed, on critical analysis and review, to reticulum cell sarcoma, neuroblastoma, metastatic carcinoma, eosinophilic granuloma, etc.

Of the original 179 there remain 91 cases with histologic proof that is acceptable to our pathologist on recent review.\* These 91 cases have been selected for detailed analysis and form the basis of this report. Twenty-seven of this group have been registered with the Bone Sarcoma Registry of the American College of Surgeons and have been classified by them as Ewing's tumor.

For the determination of prognosis and end results only the 73 cases admitted between 1918 and 1942 are considered in order to allow for the lapse of a minimal interval of 5 years in determining survival rates.

#### ETIOLOGY

*Sex.* The general belief that males are afflicted about twice as frequently as females is supported by study of our 91 cases in which 63 or 69% were males and 28 or 31% were females. (Chart I.)

*Age.* In the present series ages range from 5 months to 36 years, with an average age of 15 years for the group as a whole. In the 63 male patients the average age was 16.1 years and in the 28 females it was 12.4 years.

It is readily apparent from Chart I that the peak incidence of Ewing's sarcoma is in childhood and the adolescent years. It is striking that in only four cases of the entire series was the patient 30 years of age or older at the time of onset of symptoms, and that the oldest patient was only 36 years old. It is our belief that a diagnosis of Ewing's sarcoma in a patient over 35 years of age is open to question on the basis of age of the patient alone.

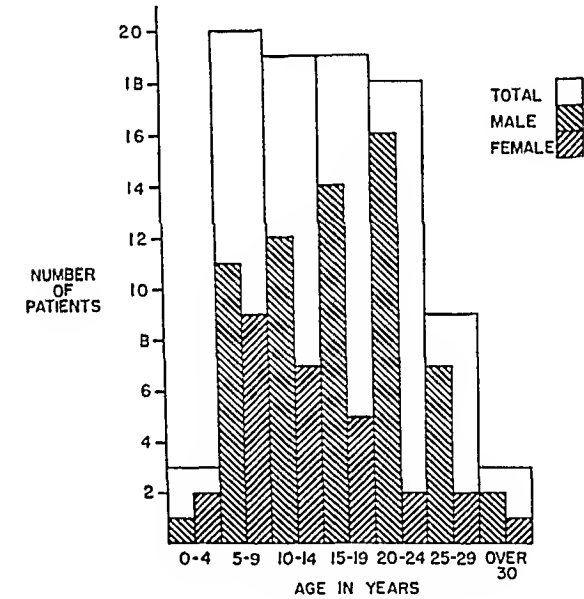
*Trauma.* An occasional case of malignant bone tumor is reported from time to time in which trauma appears to have been a significant etiological factor. It is probable that trauma in many instances focuses the attention of

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\* The authors are deeply grateful to Dr. Fred W. Stewart and Dr. Frank W. Foote for reviewing the microscopic pathology in all the cases included in this study.

physician and patient alike on a bone already harboring a tumor, a circumstance referred to by Ewing as traumatic determinism, and it is incorrectly assumed to be the cause of the lesion. In fact, it is seldom that all of Segond's six postulates<sup>69</sup> in establishing a traumatic relationship are satisfied in any given case and the postulates are not adequately satisfied in any of the cases in the present series.

In 41 cases of this series there is no recorded information concerning the presence or absence of trauma and in 15 others trauma was specifically denied. Of the remaining 35 cases, seven alleged that a fall on, or a blow to, the part initiated symptoms after a short interval, while in 12 there was an interval of from two months to seven years between the alleged injury and the onset of symptoms. The described injury was vague or indefinite as to manner incurred and as to time relationship to the onset of symptoms in 16 cases. (Table I.)



AGE AND SEX INCIDENCE OF 91 CASES EWING'S SARCOMA

CHART I.

*Infection.* In his original description of this disease Ewing remarked on the presence of an associated or antecedent febrile illness. Subsequently he expressed the view that if the theory of the bacterial cause of cancer had any foundation in fact then endothelioma (as well as lymphosarcoma) should provide the most fertile field for discovery or proof. We share this premise and are inclined to the belief that some obscure infection, perhaps virus in nature, may be found to be a factor in the development of Ewing's sarcoma. It is a common observation that the early signs and symptoms of Ewing's

sarcoma suggest an underlying infectious process and Connor,<sup>15</sup> in a review of the registered cases, reported 40% with a distinct history of early signs pointing to inflammation as an etiologic factor. He further showed that the histologic appearance of tissue seen in these cases may be indistinguishable from inflammation of bone. Meanwhile the actual causative factors of this form of bone sarcoma remain completely obscure.

An associated infection was noted in the history of 11 of our cases. There were three upper respiratory infections, two sore throats and three exanthemata.

ANATOMIC SITE

The site of the primary tumor is known in all 91 of our cases. Reference to Figure 1 will disclose the frequency with which the various parts of the



skeleton were involved in this series of cases. It will be seen that the femur, the primary site in 23 cases, was the most frequently involved bone. The bones of the skull and face, the carpal bones, the metacarpal bones, the ischium, and the phalanges were in no case the site of primary bone involvement. Bones of the right side of the body were involved primarily in 48 cases, those of the left side in 40 cases, the sacrum being the only unpaired bone found as a primary site in the remaining three cases. The bones of the

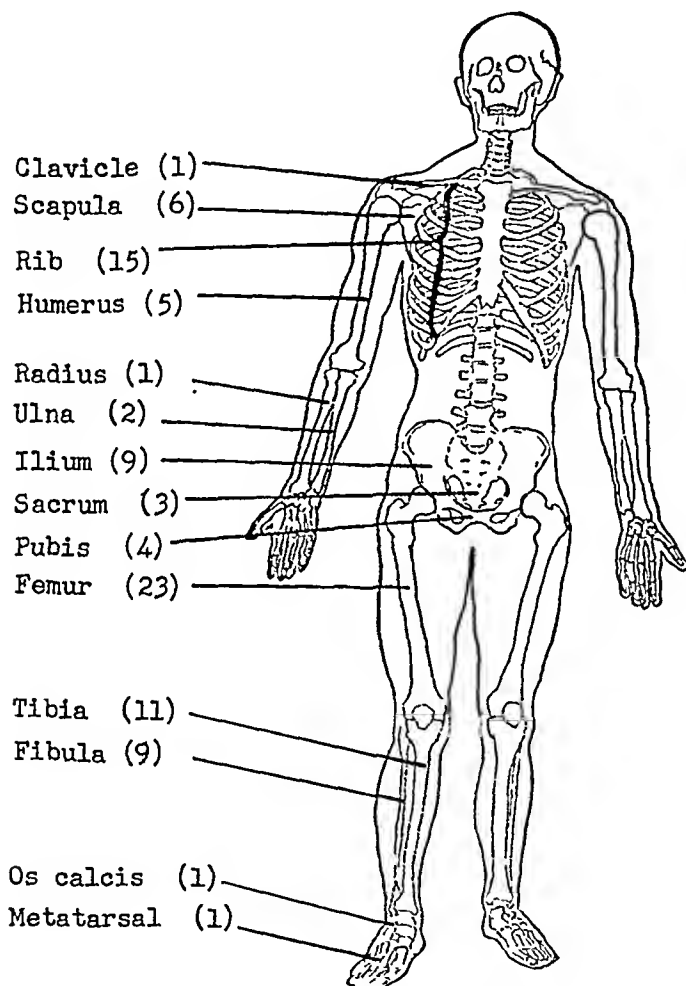


FIG. 1.—Anatomic site of primary lesions.

upper extremity were primarily involved in 15 cases, the bones of the lower extremity in 45 cases, and those of the pelvic girdle in 16 cases. All of the ribs except the first, second, and twelfth were, in one or more cases, the site of the original tumor in a total of 15 cases.

#### SYMPTOMS

Ewing's sarcoma differs little from other malignant bone tumors in symptomatology. Pain, swelling and disability constitute the major triad and, in Ewing's sarcoma, fever may be an important additional symptom.

(Table II.) A review of the present series merely emphasizes the well recognized importance of pain, and especially pain at rest, as an indication of the presence of an expanding bone lesion and supports our admonition that persistent pain in any bone calls for a tentative diagnosis of a malignant bone tumor and thorough investigation of the case clinically, roentgenologically and histologically.

*Pain.* Because of deplorable incompleteness of the medical records, no statement as to the presence or absence of pain is made in 13 of the 91 cases. However, 74 patients complained of pain in the affected part, and six of these offered this as their only complaint at the time of their first visit to the clinic. Pain was usually described as aching or boring in character and not particularly relieved by rest. Severity varied considerably from a seemingly mild degree to such intensity as to require opiates for relief. The

TABLE I  
*Antecedent trauma in 91 cases of Ewing's sarcoma*

	No. of patients
Trauma specifically denied .....	15
No statement as to trauma .....	41
Antecedent trauma recorded .....	35
Definite trauma at onset of symptoms.....	7
Definite trauma with stated interval .....	12
Indefinite trauma .....	16
Total .....	91

TABLE II  
*Symptoms in 91 Cases of Ewing's Sarcoma*

	Present	Denied	Not Stated
Pain .....	74	4	13
Deformity or swelling .....	63	3	25
Disability .....	31	5	55
Fever .....	15	7	69

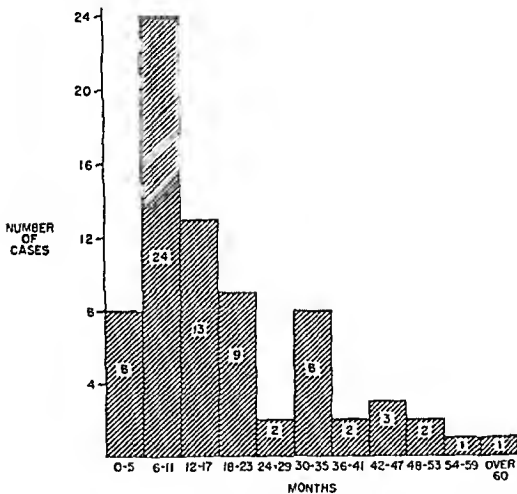
severity appeared to depend upon the location of the lesion, involvement of contiguous structures, the presence of pathologic fracture, or the individual threshold for pain. In only four cases was pain specifically denied. But of the 74 patients complaining of pain 43 described it as their first symptom and 21 mentioned it secondarily to some other initial symptom—notably swelling (Table II.) In general pain is worse at night, is unrelieved by rest and, while it may be intermittent in the earliest stages of the disease, rapidly increases in persistence and severity.

*Swelling.* If swelling is not the initial symptom, it usually follows the onset of pain promptly and in proportion to the amount of pain. In this series 63 patients complained of tumefaction in the affected part, three noticed no swelling or deformity, while in the remaining 25 case records no statement is made relative to a complaint of swelling. (Table II.) Swelling was the only complaint in six cases, 18 patients described it as their initial symptom, while 17 patients noticed swelling coincident with other symptoms—usually pain.

*Disability.* With most bone tumors disability, or loss of function, is a common secondary complaint. However, the disability appears early in Ewing's sarcoma and increases in proportion to the degree of pain and swelling which, *per se*, produce the disability. The pain resulting from movement of muscles and tendons over the tumor contributes to the disability which is enhanced by the protective mechanism of neighboring joints seeking to maintain the physiologic position of rest. A patient suffering the type of pain characteristic of this disease will invariably favor the affected part and will accordingly experience loss of function.

All but two of the 31 patients complaining of loss of function had primary involvement of the bones of the pelvis or lower extremity so that disability in walking or standing was complained of as might be expected. Two patients had a pathologic fracture to account for their disability when first seen in the clinic.

*Fever.* As a subjective complaint fever, with or without chills, was noted in 15 of the 91 cases, it was specifically denied in seven cases and was uncertain or not stated in the remaining 69 cases. (Table II.) A rib was the primary site of involvement in six patients who complained of fever and in three of these fever was the only complaint on admission to the clinic. Subsequent febrile attacks were not uncommon and, in a treated case, may be the first warning of local recurrence or metastasis.



SURVIVAL BY HALF-YEARS FROM TIME  
OF DEFINITIVE TREATMENT TO DEATH  
CHART II.

*Miscellaneous.* Numerous and variegated concomitant complaints are to be anticipated in a highly malignant tumor of this nature and depend largely upon the site of the primary tumor. Thus, symptoms of cough, shortness of breath, chest pain and voice change were presented in cases with primary rib involvement and are to be expected in patients with pulmonary metastases. Anorexia was complained of by two patients and 19 patients mentioned weight loss varying from two to 40 pounds over time intervals varying from two months to two years. Loss of weight is not unusual with any patient harboring a malignant tumor. It should not be regarded as an early symptom, and is more apt to ensue from lack of sleep and loss of appetite resulting from pain and disability than from actual tumor growth.

#### PHYSICAL FINDINGS

In the local examination it is important to note the color and texture of

the overlying skin, the presence of local heat or tenderness, the existence of a palpable tumor and its mobility in relation to the bone and the position of rest assumed by the patient to obtain maximum comfort. The complete general examination should include a search for involved lymph nodes, bone or soft part metastases, and recording of clinical temperature in addition to the laboratory studies described below.

Several of our cases had received preliminary treatment elsewhere so that a description of the early findings was not always available. However, data sufficient to be of statistical value were obtainable in 86 of the cases.

*Palpable Tumor.* Of the 86 cases in which some information is provided 54 patients presented a palpable tumor and nine presented no demonstrable tumor or swelling in the affected part. Of the remaining 23 patients 14 had been treated surgically elsewhere (amputation or resection) and nine had been treated with roentgen rays or radium and no palpable tumor was found on admission to this clinic. The tumor was described as being dis-

TABLE III  
*Physical Findings in 91 Cases of Ewing's Sarcoma*

	Present	Absent*	Not Stated
Palpable tumor .....	54	32	5
Tenderness .....	15	19	57
Local heat .....	6	4	81
Local redness .....	2	7	82
Temperature elevation .....	52	30	9
Limitation of motion .....	12	7	72

crete, regular, smooth and fusiform in shape in 12 cases, as nodular in three cases, and diffuse or indefinite in five cases. The consistency of the tumor was variously described as being firm, moderately hard or bony hard in 38 cases and as soft and fluctuant in three cases. (Table III.)

It should be borne in mind that actual bony swelling due to tumor growth is usually noted early but may be masked by an attendant soft part atrophy of disuse due to disability. Thus inspection and circumferential measurements might be misleading but careful palpation will frequently reveal the existence of actual bone enlargement or swelling.

*Tenderness.* Local tenderness was elicited in 15 patients of this series. It was specifically absent in 19 patients and no comment was made regarding tenderness in the remaining 57 patients.

*Local Heat and Redness.* In this series local heat was present in six cases and absent in four. Local redness was described in two patients and absent in seven. No mention is made of the presence or absence of these findings in the remaining cases. In view of the fact that Ewing's sarcoma may resemble acute infection of bone, the evaluation of the findings of local tenderness, redness and heat may have considerable significance in the differential diagnosis and, while sometimes present in Ewing's sarcoma, they are not apt to be as marked as in inflammatory lesions.

(\* Note: 23 patients had previous treatment elsewhere and might be expected to have altered physical findings.)

*Limitation of Motion.* In any painful lesion of bone considerable voluntary limitation of motion is to be expected. The limitation, however, is seldom if ever mechanical as actual joint involvement is rare even with extensive disease. In 12 of our cases it was noteworthy while in seven cases there was no limitation. No mention is made regarding this finding in the other 72 case records.

*Fever.* The presence of an elevated temperature in Ewing's sarcoma is frequently enough encountered to warrant its consideration as an important physical sign. It may occur with the onset of symptoms when the tempera-



FIG. 2. — Roentgenographic appearance of early subcortical lesion of Ewing's sarcoma of the left ulna in a 17-year-old female.

ture chart may closely resemble that of an acute inflammatory process in bone or it may be the first and only sign of local recurrence or metastasis. A temperature elevation above 100° F. was observed in 52 patients in our series during their hospitalization. Of these there were 27 who presented various complications such as fungating wounds, cord bladder, pulmonary metastases, etc., which, of themselves, might account for the elevated temperature. There was no obvious explanation for the elevated temperature in the other 25 cases other than the tumor itself. Thirty patients had no recorded temperature above 100° F. during their hospital stay although 5 of them complained of chills and fever, and there is no record of the temperature in the 9 remaining cases who were never hospitalized.

#### LABORATORY FINDINGS

*Roentgenographic.* Ewing's sarcoma is generally believed to present a characteristic roentgenographic appearance. The classical findings are those of an osteolytic lesion of bone irregular in outline, apparently of central or subcortical (Fig. 2) origin and rapidly involving the entire circumference when arising in a tubular bone (Fig. 3). There is "onion-peel" appearance of the overlying periosteum which is due to reactive bone formation rather than tumor invasion and imparts a fusiform shape to the tumor. Later there may be an associated soft part involvement visible on the roentgenogram.

This typical appearance is not always found and was noted in only 12 of the patients in this series while a close resemblance was described in 12 additional cases. In 16 cases the roentgenogram of the early initial lesion was unavailable or unsatisfactory for interpretation. In the remaining 51 cases the report on the roentgenographic examination was non-informative

or the appearance more closely resembled some other condition such as osteogenic sarcoma, reticulum cell sarcoma, inflammatory disease, etc. (Fig 4a.)

The diaphysis of long bones is usually the primary site of involvement but occasionally the metaphysis may be the site of origin. A study of the early roentgenograms available in 45 cases in which the tubular bones were involved revealed origin in the diaphysis in 37 cases (82%) with early spread of the disease to the metaphysis in 8. The disease began in the metaphysis in



FIG. 3.—Classical appearance of Ewing's sarcoma involving the upper shaft of the femur in a 27-year-old male.

8 cases (18%) with early spread to the diaphysis in 1 case. Later in the course of the disease nearly the entire bone may become involved.

Atypical and varied findings are to be expected in the flat bones (25% of the cases) and even in the long bones unusual and bizarre appearances may present themselves to the extent that pathologic examination is necessary to establish a diagnosis (Fig. 4a).

*Blood Studies.* The blood levels of calcium, phosphorus and phosphatase are always desirable in the evaluation of bone lesions. In Ewing's sarcoma

these values are seldom abnormal. In the late stages of the disease with rapid and extensive bone destruction the calcium might be elevated. If pathologic fracture has occurred some rise in phosphatase may occur as a result thereof although a slight elevation in the phosphatase level may be found in Ewing's sarcoma.

Serology should also be obtained in all patients with a bone tumor as syphilis is protean in its manifestations and may resemble any type of tumor particularly Ewing's sarcoma. Serologies were recorded in 27 of our cases and were negative in every instance.



FIG 4. (a.) — Ewing's sarcoma of the right tibia in a 30-year-old male. Unusual roentgenographic appearance resembling fibrous dysplasia or reticulum cell sarcoma.

Because Ewing's sarcoma may resemble inflammatory bone disease in many instances the white blood count may have considerable significance. While leukocytosis may occur it is not as apt to be as marked in Ewing's sarcoma. In our series of 91 cases white cell counts are recorded in 67 and a total white cell count in excess of 10,000 was present in only 26. Some of these elevations in cell count might well have been due to coincident conditions such as infected or fungating wounds, pulmonary metastases with pneumonitis, etc. However, 12 of the 26 patients, or 18% of the 67 cases, presented no recognized cause for the leukocytosis other than the presence of the tumor. In these cases the leukocytosis varied from 10,000 to 13,800 with no significant variation in the differential count.

*Histology.* Aspiration biopsy, or, if necessary, formal biopsy prior to any form of therapy is necessary in all cases to establish the diagnosis beyond all doubt. All 91 cases in this series had pathologic examination of representative tissue and have been classified by the pathology department of Memorial Hospital as Ewing's sarcoma.

The histologic picture of these cases is that of a neoplasm showing, in areas, crowding of cells in broad sheets and, in other areas, relatively few cells surrounded by a loose, often vacuolated, cytoplasm, often with areas of necrosis, degeneration and hemorrhage. Cells may occasionally be seen in pseudo-rosette arrangement. The cell itself is characterized by a round or ovoid nucleus with one or more nucleoli and frequently a poorly delimited cell membrane. Leukocytic infiltration is common and is sometimes of such a degree as to obscure the true underlying neoplastic nature of the lesion (Fig. 4b).

DIAGNOSIS

Ewing's sarcoma may simulate other malignant bone tumors as well as certain non-neoplastic lesions of bone. Of the former, the most important are osteolytic varieties of osteogenic sarcoma (Table IV), reticulum cell sarcoma of bone and metastatic neuroblastoma. The roentgenographic find-

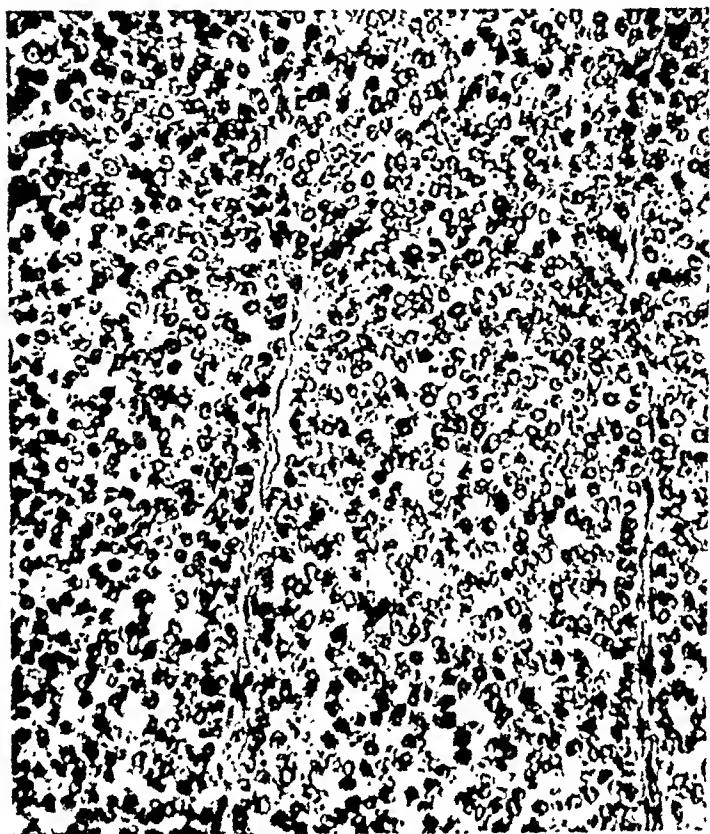


FIG. 4. (b.)—Same case. Characteristic microscopic appearance of Ewing's sarcoma.

TABLE IV  
*Roentgenographic Differential Diagnosis  
between Ewing's Sarcoma and Osteogenic Sarcoma*

<i>Ewing's Sarcoma</i>	<i>Osteogenic Sarcoma</i>
1. Location—usually in diaphysis	1. Location—usually in metaphysis
2. Expands shaft	2. Fails to expand shaft
3. Extent—usually more than half the length of the bone	3. Extent—involves less than half the bone
4. Osteolytic	4. Usually osteoblastic
5. New bone is reactive and laid down parallel to the long axis of the bone	5. New bone is largely "tumor bone" and is laid down irregularly often radiating at right angles to the long axis

ings are significant. Those characteristic of this type of tumor are extensive involvement of the shaft, and irregular cortical destruction associated with subperiosteal reactive new bone formation, giving rise to the laminated or "onion skin" appearance. This picture in some instances may be closely approximated by osteomyelitis; in fact the diagnostic difficulty is increased when fever and leukocytosis are present. Eosinophilic granuloma in its early stages may also offer difficulties in roentgenographic interpretation although the symptoms here are usually milder and the bulky soft-part tumor is lacking.



Owing to the difficulties of establishing a diagnosis based on clinical and roentgenographic criteria alone, we feel that every suspected case should have microscopic confirmation. Furthermore, since even mild exposures to roentgen rays may result in an incorrect and totally misleading histologic interpretation, we would emphasize the importance of performing the biopsy prior to the use of roentgen therapy. So highly radiosensitive is this tumor that even mild exposures will obliterate all recognizable features of the lesion and change the picture to one suggestive of inflammatory or necrotic tissue (Fig. 5).

While there is as yet no universal acceptance of the principle of aspiration biopsy as a means of affording material for histologic study, it is worthy



FIG 5. (a.)—Destructive lesion in upper end of left femur in a 12-year-old female. Biopsy after radiation therapy had been started was interpreted as chronic osteitis (b.) Unusual course of the disease prompted a second biopsy  $1\frac{1}{2}$  years later which revealed Ewing's sarcoma. Patient died of multiple metastases six months after the second biopsy.

of note that this method has proved most successful in establishing the diagnosis of Ewing's sarcoma. In 42 cases of this disease<sup>73</sup> in which it was employed, the pathologist was able to make a specific diagnosis in 31, and to report six additional cases as malignant tumor. We must concede, however, that in most clinics a biopsy by direct surgical approach will afford a safer means of identifying the suspected lesion. If a surgical biopsy is performed the wound should always be closed in layers without packing or drainage. Should one encounter material that is suggestive of pus, cultures should be taken but the possibility of Ewing's sarcoma should not be excluded until sections have been studied by the pathologist.

### TREATMENT

Two patients in this series, after examination and diagnosis, were referred back to their own physicians; the remaining 89 cases received some form of therapy at Memorial Hospital. In most instances more than one therapeutic agent was employed. These will be considered in turn, and the comparative value of the various methods will be discussed with the end results.

*Surgery.* In this series of 91 cases 115 surgical procedures were carried out. The majority of these were incision and drainage (performed under the mistaken diagnosis of osteomyelitis), open biopsies, and aspiration biopsies, and were employed for purposes of diagnosis rather than for therapy. There were, however, 33 definitive surgical procedures performed in an effort to eradicate the tumor; these comprised 18 amputations and 16 segmental or partial resections.

*Roentgen therapy.* In this series, 69 patients received roentgen therapy to the primary tumor. Since there have been many changes and advances in this field in the past thirty years, the treatment administered in each individual case naturally reflects the equipment and technic in vogue. Thus the early cases were treated empirically in terms of time of exposure to beams of unknown intensity. The majority, however, were treated with multiple converging ports and fractionated doses with high voltage machines (200 KV or 250 KV), usually at target-skin distances of 50 or 70 cm. The size and number of the ports varied with the particular lesion being treated. It is impossible to state with any degree of accuracy the total skin doses thus administered. Furthermore, it is the tissue (or tumor) dose which is the important factor to consider and this could not be estimated from the data available. Only one patient received 1000 KV therapy.

The initial response of the lesion, when recorded, was in every instance clinically gratifying and serial roentgenograms revealed evidence of bone regeneration in most cases.

*Radium.* Radium was administered in 32 cases. This was usually in the form of surface irradiation from a 4-Gm. radium element pack placed at 6 to 10 cm. distance, the size and number of the surface portals varying with the particular lesion being treated. In two cases gold filtered radon seeds were inserted into the tumor, and another patient received small quantities of radium chloride intravenously. The clinical response in most instances was similar to that obtained with roentgen therapy.

*Toxins.* Fifty-five patients in this series received one or more courses of Coley's Toxins (the mixed toxins of erysipelas and *Bacillus prodigiosus*, Shear's filtrate, etc.). A course usually consisted of from 10 to 12 intramuscular and intravenous injections beginning with a dose of a fraction of a minim and progressively increasing in accordance with the patient's response to each injection. No one in this series was treated with toxins alone. From the data available it is difficult to evaluate objectively the exact effect

of the toxins on the disease but it is our belief that Ewing's sarcoma is one type of malignant neoplasm that shows a favorable response to Coley's toxins when used in conjunction with other therapeutic agents.

*Miscellaneous.* In the earlier years covered by this series one patient was treated with intravenous injections of colloidal lead, and in later years three patients received small quantities of radioactive phosphorus. In each instance these medications were employed experimentally and in conjunction with other methods. No unusual benefits were noted.



FIG. 6. — Pathologic fracture through primary Ewing's sarcoma of the femur 8 months after radiation therapy had been instituted. High thigh amputation was done but patient died with multiple metastases 10 months after amputation.

*Pathologic Fracture.* The occurrence of pathologic fracture in Ewing's sarcoma has not been emphasized by most writers. As with any osteolytic lesion of bone this complication might be expected to occur not infrequently. In the present series of 91 cases a pathologic fracture occurred in 19 or 21 per cent. Six of these had occurred shortly before the time of admission or were discovered at the actual time of admission. In 14 of the 19 cases the pathologic fracture occurred through the site of the primary bone lesion (Fig. 6) while in the remaining five it occurred at the site of osseous metastasis from a primary lesion elsewhere. Only one pathologic fracture was encountered in the humerus. The remaining 18 all occurred in the bones of the spine, pelvis, or lower extremity where weight-bearing probably served as a precipitating factor. The incidence of pathologic fracture and the bone involved is recorded in Table V.

*Local Recurrence.* In this series there were 18 patients who presented either a microscopically confirmed, or clinically unequivocal, recurrence at the site of the primary lesion from two months to three years following the institution of therapy to the primary lesion. An analysis indicates that in eight cases the recurrence may have resulted from an inadequate dose of roentgen rays or radium. This statement is made after a very rough approximation of the amount of irradiation apparently administered to these eight patients plus a comparison of these values with the arbitrary values determined by Woodard and Coley<sup>55</sup> for the sterilization of Ewing's sarcoma. Judging by the same standard five of the remaining patients seem to have had an adequate tissue dose administered but the skin portals are believed to have been inadequate to cover the entire extent of the underlying tumor. The last 5 patients in this group seem to have had local recurrences as a

result of inadequate surgery; two had simple rib resections instead of chest-wall resection for tumor of a rib, two had high thigh amputation and one had a mid thigh amputation for tumor of the femur, instead of hipjoint disarticulation.

*Neurologic Disorders.* As a result of cerebral or spinal metastases neurologic disorders occurred with sufficient frequency to warrant discussion as a separate, frequent complication. Fifteen patients (16 per cent) of this series had objective evidence of a neurological lesion at some time during the course of their illness. Two patients with primary Ewing's sarcoma of the sacrum had symptoms and signs of sacral root involvement evidenced by urinary retention, constipation, and lower abdominal or leg pain. Eight patients had complete paraplegia believed to be due to a transverse myelitis

TABLE V  
*Pathologic Fracture in 19 Cases*  
(series of 91 cases of Ewing's sarcoma)

Bone Involved	Cases
Femur .....	10 (one metastatic)
Vertebra .....	3 (all metastatic)
Tibia .....	2
Rib .....	2
Humerus .....	1 (metastatic)
Pubis .....	1
Total .....	19

in the dorsal cord produced by metastasis. One of these patients also had loss of vision and an ophthalmoplegia, another had a right facial paralysis in addition to his paraplegia, and another had facial paralysis and inability to swallow. One patient developed a quadriplegia. The remaining two had urinary retention with episodes of incontinence believed to be due to lower cord metastases. All of these patients were, of course, in the terminal phase of their disease and none survived for long.

*Miscellaneous.* There were a variety of complications exhibited by isolated cases. One patient with a primary rib lesion developed an empyema, and another apparently died of asphyxia from massive local disease. One patient, with a primary Ewing's sarcoma of the sacrum, had a "spontaneous pneumothorax" believed to be due to extensive intrathoracic metastases. One patient, with a primary femoral lesion, developed thrombophlebitis in the affected leg.

#### METASTASES

More consistently than is so with any other type of bone neoplasm, Ewing's sarcoma is apt to metastasize early and to produce wide dissemination of the disease. In 11 of this series of 91 cases there was no available information concerning the occurrence or location of metastases; all died of the disease and probably did have metastases that were unrecognized or were not apparent at the time of last examination. Six additional cases are either

alive and free of disease or have died of other causes without known metastases. The remaining 74 cases have been analyzed and provide information regarding the location and behavior of metastases.

*Anatomic location.* Since autopsies were performed in only 14 of the cases, the anatomical site of metastases herein tabulated is based on clinical, roentgenographic and only occasionally, on pathologic (biopsy and autopsy) examination (Table VI). In 47 cases the lungs were found to be involved by metastases, usually multiple and discrete. Next in order of frequency was

TABLE VI  
*Location of Metastases*  
(based on clinical findings in 74 cases of Ewing's sarcoma,  
dead or living with disease.)

Site	Cases
Lungs .....	47
Skull and scalp .....	32
Vertebrae .....	21
Bones of pelvis .....	20
Lymph nodes:	
Groin .....	9
Axillary .....	4
Supraclavicular and neck .....	3
Femur .....	16
Humerus .....	14
Orbit .....	11
Ribs .....	9
Pleura .....	9
Intracranial .....	8
Abdominal viscera .....	6
Tibia .....	5
Mandible .....	4
Skin and soft parts .....	4
Mediastinum .....	4
Scapula, clavicle, radius, sternum and fibula, one each .....	3
	5

the skull and scalp which showed metastases in 32 cases. The bones of the pelvis were involved in 20 cases, the spinal column in 21, the femur in 14, and the humerus in 11 cases. Many other sites were occasionally involved by metastases as indicated in Table VI. It is obvious from this study that the next most common site for metastases, after the lungs, is the other bones of the skeleton, and that the lymph nodes and viscera were believed to be involved in only five instances.

As has already been stated the occurrence of neurological complications in Ewing's sarcoma is more frequent than chance alone would allow. The vertebrae were involved by metastases in 21 instances, and the intracranial region in 6, each of which might have induced neurological complications. The occurrence of metastasis to the bones or soft tissues of the orbit in nine cases is likewise noteworthy and one of us witnessed a case in which both eyeballs protruded from their sockets and ruptured before death.

The distribution of metastasis as determined at autopsy in 14 cases is shown in Table VII.

*Characteristics of Metastases.* On the basis of a study of 74 cases it may be said that, in general, metastases possess the same characteristics as the primary tumor. When superficially located they often present a palpable, firm, and possibly slightly tender tumor. Pain is frequently referable to the metastases. As has been suggested, the occurrence of fever in a patient that has had Ewing's sarcoma usually indicates metastases or local recurrence. The roentgenographic appearance of the metastases as well as the primary tumor is invariably one of osteolysis. Obviously the anatomical location of the metastasis chiefly determines its behavior; thus, chest metastases are often associated with cough, pulmonary suppuration, expectoration, and fever, but rarely hemoptysis. Metastases in the skull may be relatively painless while those in a vertebra may be extremely painful and associated with

TABLE VII  
*Location of Metastases*  
(based on autopsy findings in 14 cases of Ewing's sarcoma.)

Site	Cases
Lungs .....	9
Pleura .....	8
Mediastinum .....	6
Skull and scalp .....	5
Bones of pelvis .....	5
Ribs .....	5
Vertebrae .....	4
Femur .....	3
Dura .....	3
Humerus .....	3
Soft tissues .....	3
Tibia .....	2
Orbit .....	2
Retroperitoneal nodes .....	2
Liver .....	2
Pericardium .....	2
Fibula, brain, mandible, axillary nodes, diaphragm, spinal cord, one each .....	6

(Note: The peripheral bones and brain were not examined in all cases.)

radicular pain. The metastases of Ewing's sarcoma are apt to be progressively less radiosensitive as multiple areas make their appearance.

*Treatment of Metastases.* By the time metastasis has occurred in Ewing's sarcoma the chances of a cure are nil. For this reason probably, and because of the extreme radiosensitivity of these lesions, the treatment of metastases in this series has been practically confined to roentgen therapy. Of the 74 cases presenting metastases, no treatment was administered to the secondary lesions in 20 cases because the metastasis was relatively asymptomatic or because the patient was in the terminal stages of the disease. In the remaining 54 cases the following methods were employed: roentgen therapy in 42 cases, radium element pack in two cases, and both of these agents in eight cases. In the remaining two cases the metastases were treated with surgery; a thyroidectomy was performed in one under the misapprehension that a primary thyroid tumor existed, and in the other, a groin dissection was per-

formed at the time of hipjoint disarticulation for a Ewing's sarcoma of the tibia with metastasis to the groin nodes. The results obtained by all of these methods proved gratifying since in almost every instance the patient showed symptomatic improvement for a time and since there was frequent objective evidence of complete disappearance of the metastases. Whether the treatment of the metastases materially lengthened the patient's life cannot be determined, but it certainly appears to have rendered the remaining days more comfortable.

#### END RESULTS

Four patients in this series of 91 cases were lost to follow-up; all were living with disease at the time of their last examination. One other case, in which the autopsy was performed at Memorial Hospital, had but a meagre clinical record. These five must necessarily be considered as treatment failures but there is too little information available to include any one of them in an estimate of survival rates. Of the remaining 86 patients, 12 are living. One other patient (Case 3) lived for 14 years and 7 months and then died of an intercurrent episode of acute appendicitis with peritonitis but without evidence of a recurrent or metastatic tumor, so he must be regarded as a therapeutic success. The group of fatalities include 73 patients who have been followed to their death from Ewing's sarcoma.

*Deaths.* The time interval between the institution of definitive therapy and death in all 73 cases is known. The shortest interval occurred in a patient who succumbed to wide dissemination of the disease one week after admission to the hospital. The longest interval, 5 years and 7 months, was noted in a case treated with roentgen rays and thigh amputation. According to Chart II if the interval between treatment and death is analyzed by six-month periods it will be noted that more patients died during the second half-year following treatment than in any other half-year period. The average survival from the time of treatment to death in these 73 cases, however, was 18.7 months.

Autopsies were performed in 13 of the 73 cases, as well as in one other of the entire series of 91 patients (15.5 per cent). In all 14 cases a diagnosis of Ewing's sarcoma had been established by biopsy or had been seriously considered clinically. It is felt, therefore, that even where the protocols fail to mention it, a careful search was made in each instance to uncover unsuspected clinical evidence. No finding is recorded that is at variance with the clinical diagnosis of primary Ewing's sarcoma of bone. Other than the primary tumor and its metastases there were no constant autopsy findings recorded, except that the majority of patients appeared to have had bronchopneumonia, atelectasis, or pulmonary edema which, in these cases, was believed to be the immediate cause of death.

*Living Patients.* Twelve patients in this series are living. Seven of these are now alive with evidence of dissemination of disease which either is

under treatment or appears to be temporarily under control. Five patients are living and well without evidence of recurrence or metastasis.

*Five-year survival.* For the purpose of computation it is obvious that the twenty-five year period from 1918 through 1942 must be employed. Of the 73 patients who were first examined at Memorial Hospital during this period, only 3 lived without evidence of recurrent or metastatic disease for a period of five or more years following the institution of definitive therapy. Two of these patients are alive and well today  $6\frac{1}{2}$  years and 12 years follow-



FIG. 7. (a.) (Case 1)—Atypical appearance of Ewing's sarcoma in lower end of left fibula. Ewing made the diagnosis on open biopsy. (b.) Roentgenogram 5 years after resection of tumor bearing segment of fibula with stabilization of the mortise by means of 2 vitallium screws which were subsequently removed.

ing treatment. The third patient lived for  $14\frac{1}{2}$  years following treatment and then died of acute appendicitis with peritonitis but without evidence of a recurrent or metastatic tumor.

#### CASE REPORTS

Case 1.—B. C., aged 22, was admitted to the Ruptured and Crippled Hospital on June 11, 1941, complaining of a "lump" just above the left ankle of  $1\frac{1}{2}$  years duration attributed by the patient to a kick. He complained of moderate pain in



this area ever since the injury. Prior to admission, an open biopsy had been performed elsewhere and 10 roentgen ray treatments had been administered. On June 12, 1941, resection of the lower end of the left fibula was performed with fixation of the remaining fragment to the tibia with screws (Fig. 7). A review of the slide of previous biopsy was reported as Ewing's sarcoma of bone. The pathologic examination of the surgical specimen showed no residual tumor present. The patient was discharged from the Ruptured and Crippled Hospital on June 30, 1941, and then referred to Memorial Hospital for further follow-up. The patient was then seen at frequent intervals and remained symptom free. On March 23, 1946, he was admitted to Memorial Hospital and 2 days later under local anesthesia, the vitallium screws were removed from the left lower leg. Since that time, the patient has remained symptom free with no functional loss. He was last seen and found to be free of disease on January 28, 1948, 6½ years after original treatment



FIG. 8. (a.) (Case 2)—Ewing's sarcoma of upper right humerus confirmed by open biopsy. Treated with roentgen rays and Coley's toxin. (b.) Roentgenographic appearance 10 years later. Patient alive and well 12 years.

Case 2.—L. L., aged 13, was admitted to Memorial Hospital on April 14, 1936, stating that one year previously he noticed the onset of aching pain in the upper portion of his right arm. The pain increased in severity during the next two months so that the patient consulted a doctor who stated that he had a tumor. On July 4, 1935, at another hospital an open biopsy was performed which substantiated the diagnosis of tumor but temporarily relieved the patient of his pain. Because of the recurrence of pain the patient was referred to this institution. Physical examination revealed a firm nodular tumor underlying the previous biopsy scar which was non-tender and which did not appreciably interfere with the function of the arm. A review of the biopsy sections was reported as showing endothelioma of bone. Following his open biopsy in July, 1935, the patient had been given 1870 r x 2 high

voltage therapy elsewhere. In this institution, the patient was given 1500 r x 3 high voltage roentgen ray treatment and was then admitted to the hospital for a course of Coley's toxin. He received a total of six intramuscular injections and was discharged improved. Although the patient was symptom free and showed no signs of recurrence of the tumor, in July of 1936 he was given further high voltage roentgen ray therapy in this institution for a total of 1000 r x 3 to the right upper humerus. As a result of these two courses of radiation therapy, it was estimated that the patient received roughly 6,025 r tissues dose in the tumor. The patient has since been followed in this clinic as well as by his local physician and has remained free of disease and shows only some atrophy in the region of the right shoulder presumably secondary to his roentgen ray therapy. The patient was last examined on November 18, 1947, and found to be in excellent health without evidence of recurrent disease 12 years since first treatment. (Fig. 8.)



FIG. 9 (Case 3)—Early roentgenogram. Clinical diagnosis of osteomyelitis. Biopsy interpreted as osteosarcoma and later revised to Ewing's sarcoma. Patient remained well 14 years and died of acute appendicitis with peritonitis.

Case 3.—H. S., aged 8, was struck in the leg with a sled while at play in January, 1920. Because of persistent pain in the right ankle, roentgenograms (Fig. 9) were made and the boy was taken to the Ruptured and Crippled Hospital where, in March, 1920, an incision and drainage of the right fibula was performed under the mistaken diagnosis of osteomyelitis. Because of persisting symptom of pain, the patient returned to the Ruptured and Crippled Hospital and a right mid thigh amputation was performed in June, 1920. Eight weeks later, a right groin dissection was performed because of grossly enlarged nodes. The patient was referred to Memorial Hospital on October 26, 1920, because of a firm mass deep in the iliac fossa above the area of groin dissection. A total of 10,109 mgs. hours was administered to the right groin with the radium element pack at 6 cm. distance, with improvement. The patient was discharged from Memorial Hospital on November 6, 1920, and referred back to

TABLE VIII  
*End Results in the Series of 73 Cases of Ewing's Sarcoma treated from 1918 through 1942.*

Determinate Group—with histologic verification	
Dead .....	70
Free of disease more than 5 years .....	3
Living and well .....	2
Dead without disease after 5 years .....	1
<hr/>	
Total .....	73
Successful results .....	3
Five-Year Survival-rate .....	4.1%

the Ruptured and Crippled Hospital for the administration of Coley's toxin. Although at the time of admission, roentgenograms of the chest were reported as showing metastasis in the lungs, this finding was never confirmed on subsequent examinations. This patient was seen at infrequent intervals during the ensuing years and remained

symptom free without evidence of recurrence or metastasis. In January, 1935 14½ years later, the patient had an attack of acute appendicitis with generalized peritonitis to which disease he succumbed on January 31, 1935, without evidence of recurrence or metastasis from his original Ewing's sarcoma.

The five-year survival rate in this series of 73 cases (Table VIII) is 4.1 per cent, an extremely low survival rate, in fact somewhat lower than is commonly believed to apply in Ewing's sarcoma. It dramatically emphasizes our belief that Ewing's sarcoma is an extremely malignant lesion, one that is exceeded in poor prognosis only by leukemias.

#### SUMMARY

This report is based upon a study of 91 histologically proved cases of Ewing's sarcoma of which the end result after five or more years is known in 73 cases.

Attention is called to the predominance of the male sex, the preponderance of cases in the age-group from five to 25 years, and the simulation of an infectious or inflammatory process as evidenced by frequent febrile reaction, leukocytosis, and even by the roentgenographic appearance.

The difficulty sometimes encountered in distinguishing this disease from osteogenic sarcoma is also mentioned, with due emphasis being placed upon the importance of securing microscopic confirmation *prior* to treatment. As is pointed out, this is especially indicated because of the masking of the histologic picture following even small doses of roentgen therapy.

In young children Ewing's sarcoma may be exceedingly difficult to distinguish from metastatic neuroblastoma; in older children, adolescents and young adults, reticulum cell sarcoma of bone and angiosarcoma may also closely resemble it. The more favorable prognosis of reticulum cell sarcoma of bone and its response to doses of roentgen therapy, smaller than are required to inactivate permanently Ewing's sarcoma, makes its recognition a matter of importance.

The various methods of treatment of Ewing's sarcoma have yielded uniformly poor end results. This is amply demonstrated by the fact that only three out of 73 cases (4.1 per cent) survived five years or more. Regardless of the method employed, whether immediate surgery, preoperative irradiation, or irradiation alone or in combination with Coley's toxins, the ultimate result is practically always death from widespread metastases. Neurological complications are frequent and disturbing. No known method has as yet succeeded in overcoming the tendency of dissemination of the disease to the lungs, to other bones, and sometimes even to the lymph nodes and viscera. Ewing's sarcoma presents a challenge to the profession to devise a totally different mode of attack. In the meantime all that can be accomplished in the vast majority of cases is palliation for a period of from one to three or more years. Such palliation is usually best achieved by roentgen therapy.

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DISCUSSION.—DR. NORMAN L. HIGINBOTHAM, New York: In opening the discussion on Dr. Coley's paper I should like to emphasize some of the more important phases of this disease. The film on the screen represents one of the earliest lesions we were able to obtain, and I believe demonstrates very clearly the cortical origin of a purely osteolytic lesion. The process is just beginning to invade the medullary cavity and to set up a periosteal reaction. Formerly it was considered that this tumor was medullary in origin. After analyzing four cases similar to this one, we found that the tumor had a probable cortical rather than a medullary origin. The process goes on and eventually invades the entire cortex circumferentially.

This is a rather typical picture produced in the later stages of Ewing's sarcoma. There is diaphyseal involvement, a fusiform shape which is quite characteristic, complete osteolytic destruction of the cortex all the way around the bone, lamellation or so-called onionskin appearance of the periosteum and, as the tumor has advanced, it has produced these radiating spicules outward from the bone. This sunburst appearance was originally described as pathognomonic for osteogenic sarcoma. However, in our experience we find that it occurs equally often in Ewing's sarcoma.

Another quite characteristic appearance produced by Ewing's sarcoma is this so-called moth-eaten appearance or cracked ice appearance. Here again is observed the diaphyseal involvement, the fusiform-shaped tumor extending upwards to the metaphyseal region and leading to imminence of pathologic fracture. When pathologic fracture occurs it may complicate the roentgenologic diagnosis.

This shows a 12-year-old boy with a diaphyseal lesion, purely osteolytic; even though there is a pathologic fracture one would suspect the diagnosis of Ewing's sarcoma which was confirmed by the microscope. Considerable difficulty in differential diagnosis may occur, however. Here is a picture which closely resembles, perhaps, fibrous dysplasia, and one might think also of reticulum cell sarcoma. This is the type of case in which biopsy is extremely important. In this case the pathologic report on the biopsy was malignant tumor, probably Ewing's sarcoma. This was later confirmed and low thigh amputation was carried out. The gross specimen shows the medullary cavity from which the tumor has been removed, also the complete cortical destruction and periosteal reaction which was quite evident on the roentgenogram.

The hazard of giving radiation therapy without a microscopic diagnosis is borne out by this particular case. In this young girl the clinical and roentgenographic diagnosis was Ewing's sarcoma. A course of radiation therapy was outlined for this lesion at the upper end of the femur and we proceeded with it. Then a biopsy was done and the pathologist reported that he could find only chronic osteitis. Accordingly, we felt that an error had been made in our clinical and roentgenographic judgment and further irradiation was withheld. However, a year and a half later this picture of an obviously malignant tumor was seen, and a second biopsy confirmed the diagnosis of Ewing's sarcoma. Had biopsy been done prior to irradiation therapy, as should have been done, we feel sure we would have had the correct diagnosis at the outset. The patient died of metastases six and a half months after this picture was taken.

Dr. Coley mentioned the three five-year survival cases, and I shall review them briefly. This 22-year-old boy had a lesion of the fibula, diagnosed by biopsy as Ewing's sarcoma. Preoperative irradiation was given to this area well above and well below the actual lesion. Then resection of the tumor-bearing section of bone was carried out and the mortise of the joint was stabilized with two vitallium screws. These were removed five and a half years later. The patient is living and well six and a half years following operation and was seen just a month ago.

The second patient is a 13-year-old boy with a lesion in the upper end of the humerus, diagnosed by biopsy as Ewing's sarcoma. A total tissue tumor dose of 6000 r units was estimated to have been given upon completion of irradiation therapy. In conjunction with and following this therapy he was given a long series of injections of Coley's toxin. He was last seen in December, 1947, alive and well 13 years after the original therapy.

The third and last case is an 8 year old boy with a lesion in the lower end of the fibula diagnosed as Ewing's sarcoma by biopsy. High amputation was done and Coley's toxin was given postoperatively. This patient survived 14 years, only to die of acute appendicitis with peritonitis, although entirely free of malignant disease.

Three cases surviving a period of five years are hardly enough from which to draw any conclusions as to treatment. One might legitimately ask what is the treatment for this rather hopeless condition. It is our impression at the present time that, given a diagnosis of Ewing's sarcoma, planned treatment should include biopsy to prove the nature of the lesion, preoperative irradiation, removal of the tumor either by resection or by amputation above the bone involved, and postoperative administration of Coley's toxin.

DR. J. J. MORTON, Rochester, N. Y.: When George Peck asked me to write on treatment of this disease, there were some known facts; namely, that it is a disease of youth, that males predominate, that a great many of the lesions are below the waistline, that fever is a frequent accompaniment, and that osteomyelitis is a frequently mistaken diagnosis. Many have come to me who have been operated on for osteomyelitis; they have shown no growth of any organism, the osteomyelitis, so-called, does not improve, and the doctor begins to suspect that he is dealing with something else, and it is usually Ewing's tumor.

Since 1940 there have been two or three series reported, but none so extensive as this one from the Memorial. Dr. Myerding reported a series from the Mayo Clinic and Dr. Campbell reported a series from Memphis. The Bone Sarcoma Registry also put out a report in the forties. Those are the only series reported and, for that reason, I think this is a very important paper.

The pathology is quite confusing, although I think it is a definite entity. We have been told in the past that adrenal sympathetic tumors resemble it very closely but can be differentiated by the fact that they form rosettes. Recently, some Ewing's



tumors have been shown to form rosettes of tissue. If you stain cells for reticulum, you will find that Ewing's tumor forms reticulum also. Recently Dr. Stout told me that he was very hesitant about making a diagnosis of Ewing's tumor; that, in fact, he did not know how to do so; and he is a trained pathologist. The surgeon, therefore, has a good deal of difficulty in deciding what he is really dealing with. Nevertheless, I think Ewing's sarcoma is a true tumor because we have had enough post-mortem examinations to know that the adrenals are not involved and that this is not a lymphosarcoma. The Australians will not admit that there is such a tumor, and it is in doubt in some of the Scandinavian countries—so it is still controversial.

As to treatment, at the time I was asked to write on the subject treatment was the same as for any form of malignancy, except that the Memorial had a tremendous amount of radiation which was used on patients with this diagnosis. Dr. Ewing pushed it to the extreme, but he admitted to me that he was trying to find the best dosage to use. If you review all the literature you will find, I am sure that there are 18 or 20 patients that have gone beyond the five-year period, some considerably beyond. Treatment has been quite varied; some by surgery, some by radiation in various ways, some by a combination of agents and some by x-ray alone. There are two or three cases which have been healed by x-ray alone for a period of several years. Meyerding agrees that irradiation treatment holds the premier position, multiple cross-fire ports being used.

I agree with Dr. Coley that this is a most discouraging disease, and I hope we will find some better method of treatment.

# FURTHER EXPERIENCES WITH PERITONEAL IRRIGATION FOR ACUTE RENAL FAILURE

Including a Description of Modifications in Method

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In our last communication on this subject<sup>1</sup>, reported in this journal in November, 1946, we stated that the method of peritoneal irrigation as then developed was still in an experimental stage owing to certain inherent limitations: the formula of the irrigating fluid did not correct acidosis or hypocalcemia; the absorption of water from the irrigating fluid was not under adequate control; some protein and probably water-soluble vitamins were lost into the irrigating fluid; and most significant of all, peritonitis could not be prevented.

In this report, which is based on a clinical experience of some 14 additional patients in renal failure, we present modifications in the method which we have introduced as the lessons of our experience indicated. Analysis of the clinical data which follows demonstrates that a satisfactory degree of fluid and electrolyte balance can be achieved and recovery of renal function facilitated. The danger of peritonitis, which has been greatly minimized but by no means obviated, still constitutes the chief hazard of the technic. Even so, the results now obtainable<sup>2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12</sup> are such as to warrant continued exploitation of this method for treating acute renal failure, providing recovery of renal function is still possible.

## MODIFICATIONS IN METHOD

A. *The irrigating fluid* has been altered so that it now contains the following amounts of anhydrous substances in grams per liter: NaCl 7.4, KCl 0.2, CaCl<sub>2</sub> 0.2, NaHCO<sub>3</sub> 1.0, dextrose 10.0; plus gelatin\* 10.0 and MgCl<sub>2</sub>·6H<sub>2</sub>O 0.22.

The reasons for these changes are: (1) the NaCl is reduced to 0.74 per cent because some patients develop hyperchloremia. An even greater re-

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\*\* The work described in this paper was done under a contract, recommended by the Committee on Medical Research of the Office of Naval Research of the United States Navy and Harvard University.

† Read before the Meeting of the American Surgical Association, May 27-29, 1948, Quebec, Canada.

duction in chloride with a corresponding substitution of sodium lactate might be desirable, but the resulting greater alkalinity might prove too irritating to the peritoneum and would require an adjustment of the pH after autoclaving and cooling. The difficulty of carrying out a sterile titration procedure on large fluid volumes has deterred us from carrying out this modification. Partial substitution of NaCl by  $\text{NaHCO}_3$ , which would have the advantage of better counteracting the acidosis, would also make the fluid too alkaline.

#### METHOD OF STERILIZING PERITONEAL IRRIGATION FORMULA

CLAMPS A & D OPEN IN AUTOCLAVE, THEN CLOSED

CLAMPS B & C CLOSED

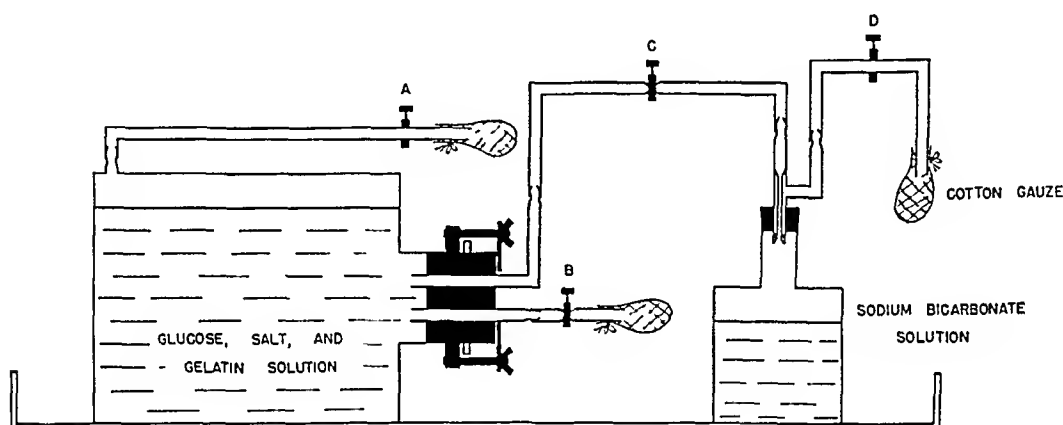


Fig. 1.

(2). The calcium ions have been doubled because the blood levels of calcium are regularly low in uremic patients and because the ionic calcium concentration requirement is higher when phosphate is elevated. Even with the increase in calcium ions, intravenous calcium therapy is still necessary. A further increase in calcium ion concentration of the irrigating solution may be worthwhile and will be tested.

(3). The phosphate is omitted because the blood phosphate concentration is excessive in uremia and because calcium and magnesium are precipitated from the irrigating solution by phosphate if their concentration or the pH is in excess of that in unmodified Tyrode's solution.

(4). To avoid absorption of water the solution is made more hypertonic by adding gelatin to a concentration of 1 per cent and by increasing the glucose from 1.5 Gm. to 10 Gm. per liter. The increase in hypertonicity might be obtained by a sufficient amount of either gelatin or glucose alone. Glucose alone in sufficient amount is possibly too irritating. The advantage of some glucose in higher concentration than we have used heretofore is

\* We are grateful to the Atlantic Gelatin Company for this material.

Fig. 2.

COMPLETION OF PERITONEAL IRRIGATION FORMULA

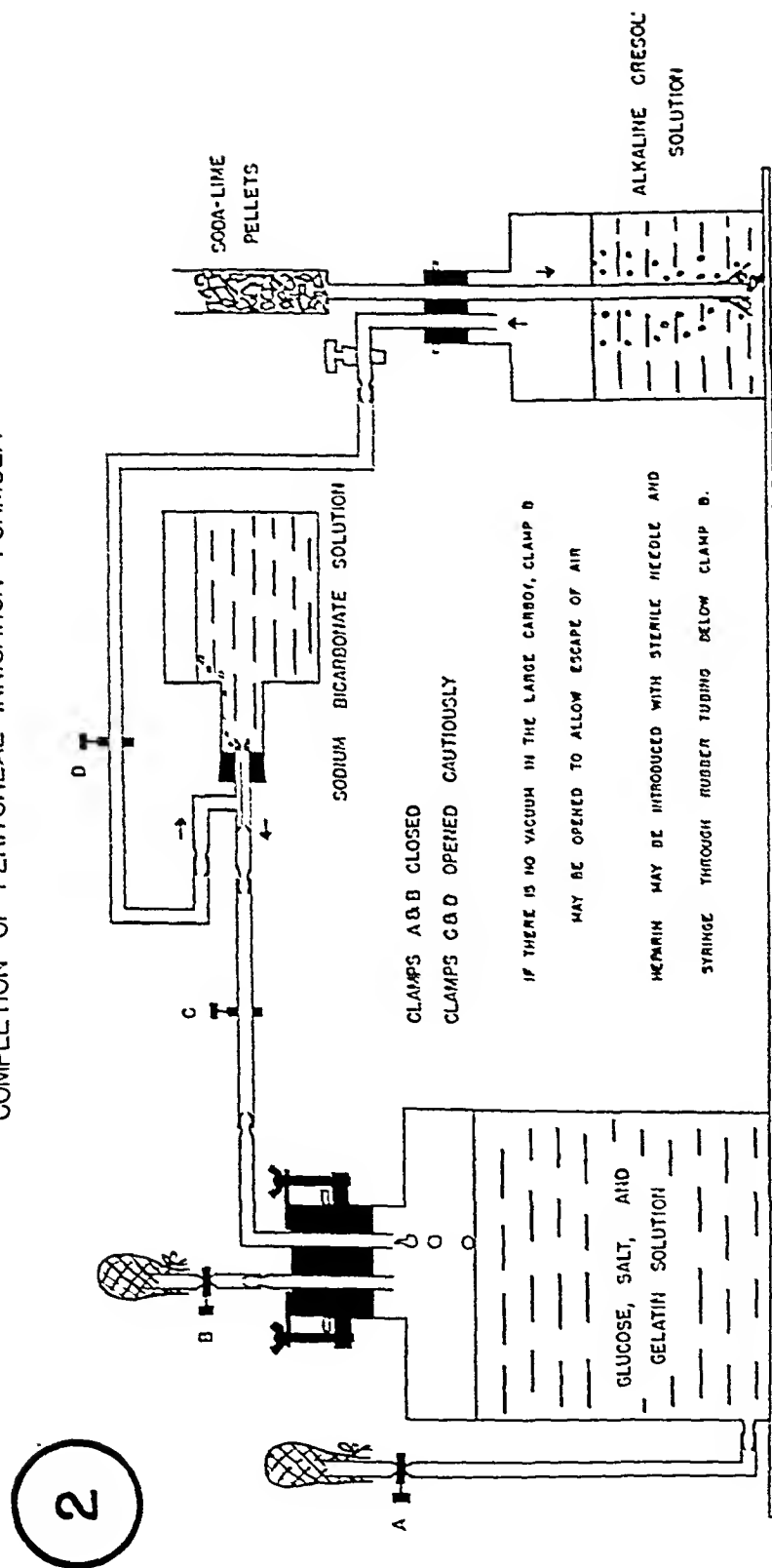
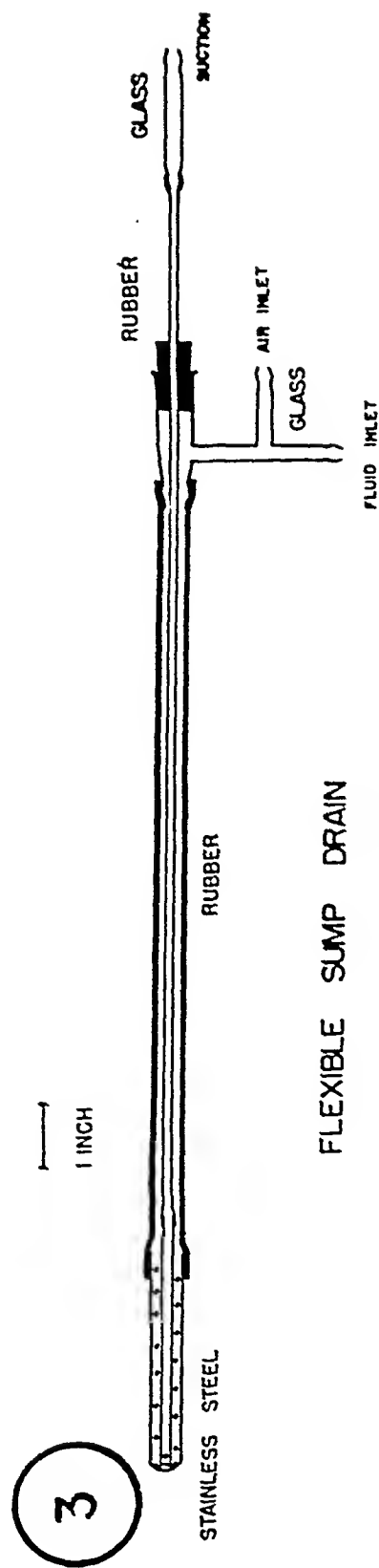


Fig. 3.

FLEXIBLE SUMP DRAIN



that it supplements the limited amount that can be given intravenously to supply the basal caloric requirement.\*\*

B. *Preparation of the Irrigating Fluid* (Figs. 1 and 2). In order to avoid contamination of the fluid after sterilization, the sodium bicarbonate, which must be autoclaved apart from the remainder of the solution, is added after cooling, by arranging the flasks in tandem during autoclaving (Fig. 1), so that the vacuum created during cooling accomplishes transfer of the bicarbonate solution to the carboy on opening the appropriate stopcocks (Fig. 2). All tubing is clamped during the cooling period. Air entering the system after cooling is bubbled through an alkaline solution of parachlorophenol and cresol. In several tests, cultures from cotton plugs filtering the air which

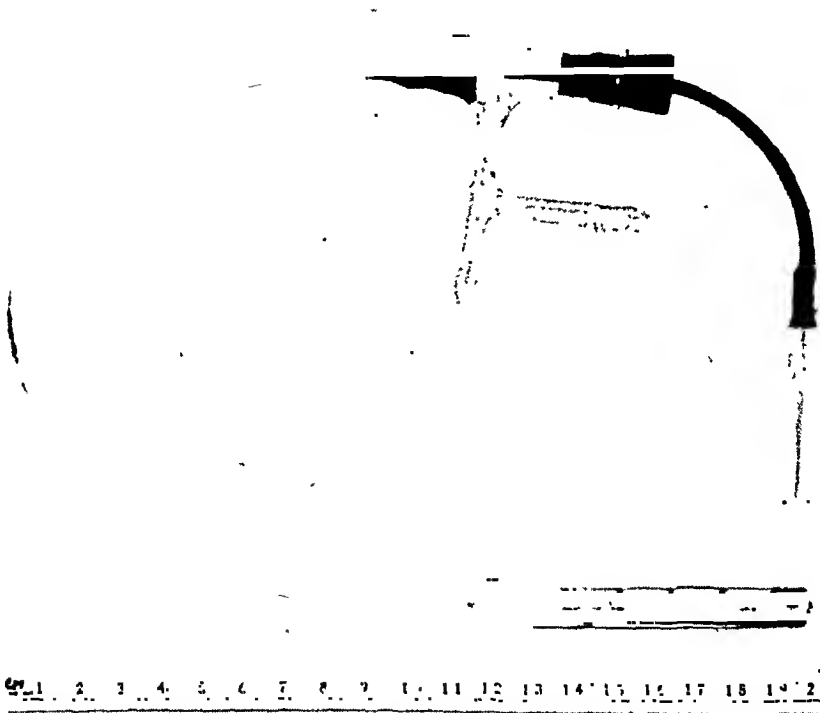


Fig. 4.—Illustrating structure and design of the flexible sump drain.

had passed through the cresol filter were found to be sterile. Cultures from samples taken at the point of entrance of the final irrigation formula into the abdominal wall are also uniformly sterile. Because the bacterial filter, formerly interpolated at this point, impedes the flow of fluid containing gelatin it no longer is used and is unnecessary since the solution is sterilized by autoclaving in the containers and connecting apparatus from which it is delivered to the patient. Heparin and penicillin, formerly added to the solution after sterilization, are now omitted.

\*\* Some 200 Gm. of glucose are absorbed in 24 hours from the irrigating fluid and the remainder (150-200 Gm) is given in a 15 per cent concentration intravenously.

C. *Irrigation Procedure.* To prevent the absorption of water it is essential that the irrigating fluid shall not be allowed to lose its hypertonicity. Recovery of the fluid before equilibration can occur is accomplished by confining the fluid to the pelvis and by the use of a flexible-shaft sump drain the three-inch stainless steel tip of which is placed in the depth of the cul-de-sac. Continuous irrigation from a separate inflow tube to the sump or intermittent filling and emptying by using the sump as a two-way system is used.

The sump drain is placed as follows: Under spinal anesthesia a short transverse incision down to the deep fascia is made beneath the costal margin. Through a short incision opposite the anterior superior spine the peritoneal cavity is opened. A subcutaneous tunnel connecting the two incisions is made. The metal end of the flexible sump drain (Figs. 3 and 4) is inserted through the upper incision and passed along the subcutaneous tunnel to the lower incision, through which it enters the peritoneal cavity, where it is placed under direct vision into the bottom of the cul-de-sac (Fig. 5). The peritoneum, fascia, and rectus muscle are closed snugly around the rubber portion of the sump drain. The skin of the lower incision is closed over the tube and the skin of the upper incision is closed around the tube, which, at this level, projects through the sterile dressing. Then it is attached to glass connecting tubes (Fig. 5), one of which connects to the fluid carboy, another to a suction line and a third to an air inlet. The suction line leads to a fluid collecting carboy and a negative pressure regulator. The air delivered to the sump drain is passed in fine bubbles through the sterilizing solution (alkaline parachlorophenol and cresol).

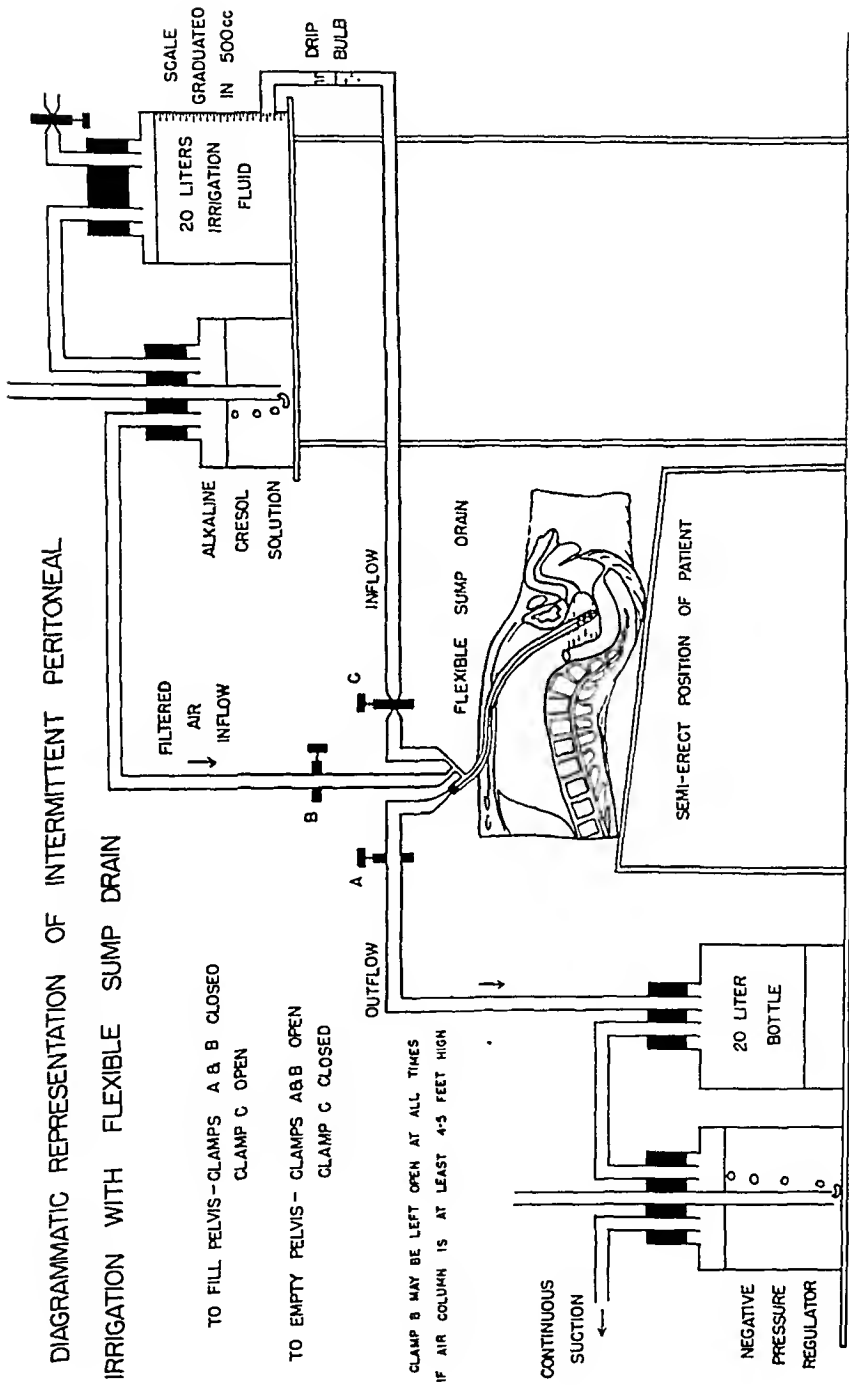
The system is operated by a series of screw clamps shown in Figure 5. About a liter of fluid is allowed to enter the pelvic cavity through clamp C, while clamps A and B are opened; and all the fluid is withdrawn into the collecting bottle on the floor at the bedside. Fresh fluid is introduced and the cycle repeated. The procedure is carried out by a nurse, who must be in constant attendance.

Samples are taken by needle aspiration daily from the sterilized outflow tube at A for study of the drainage fluid for the presence of bacteria or leucocytes. Samples taken daily from the inflow tube at C have always been sterile. Chemical analysis is done on aliquots taken from the collecting bottle.

The patient lies semi-erect, so that the fluid in the pelvis remains below the upper incision. Thus no contact by possible ebb and flow can be made between the fluid and the skin of the abdominal wall. Fig. 6, a bedside photograph, shows gastro-intestinal drainage, intravenous therapy and peritoneal irrigation proceeding simultaneously. The patient is also on constant bladder drainage, so that urine studies together with blood analyses permit accurate assessment of renal function.

Irrigation is discontinued after 72 hours, or sooner if diuresis begins. If the drainage fluid shows bacteria or more than a few leucocytes per high

Fig. 5.



power field, peritoneal contamination may be presumed to be present and the procedure is terminated at once. Even if the drainage fluid remains sterile the irrigation is stopped after seventy-two hours. This we judge from experience is the maximum period of continuous irrigation that is compatible with the avoidance of frank peritonitis. Should diuresis fail to occur thereafter, the procedure can be reinstituted upon the return of high levels of retention products or the disappearance of peritoneal irritation if present.

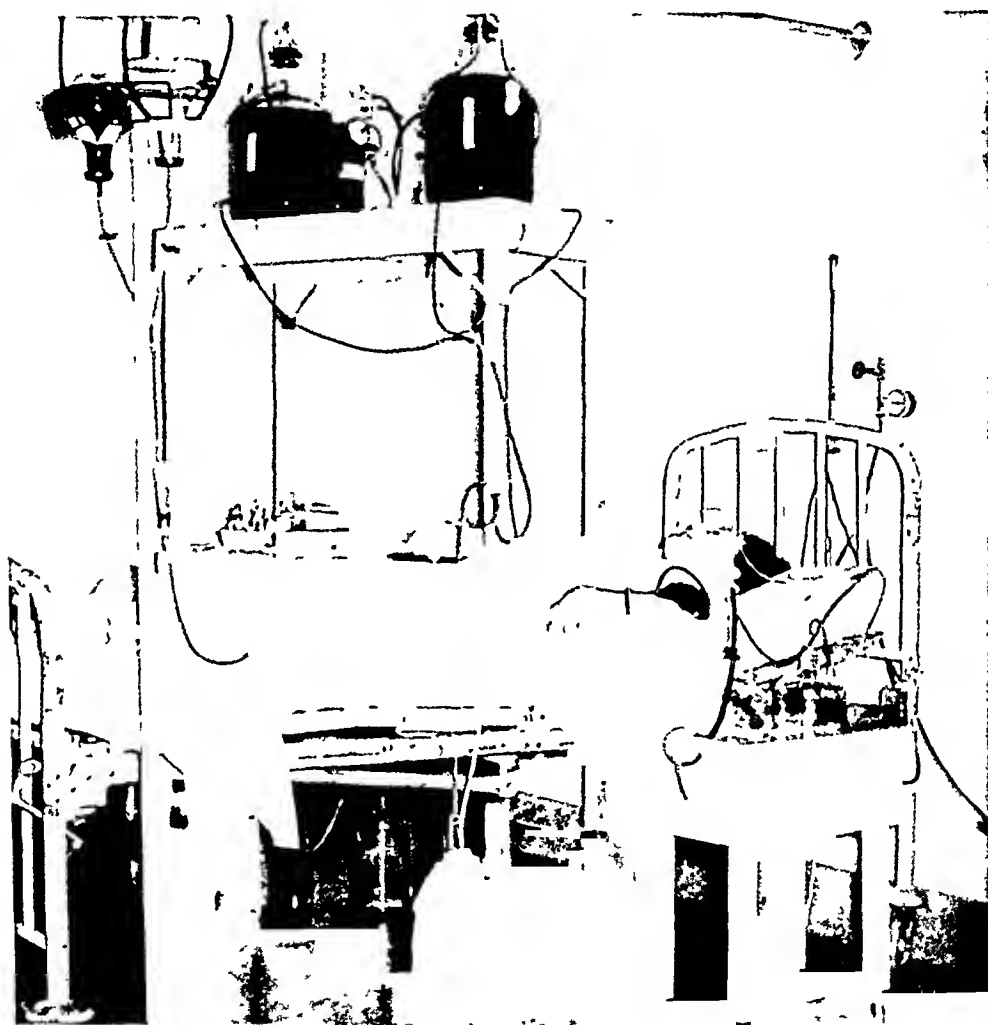


Fig. 6.—Showing gastro-intestinal drainage, intravenous therapy and peritoneal irrigation proceeding simultaneously.

Distorted gastrointestinal function (anorexia, vomiting, ileus, distention) is nearly always present in uremia, so that the patient must be intubated and all alimentation given parenterally.

Not a few patients are unwisely overhydrated beforehand, burdened with edema, particularly of the lungs, which are abnormally vulnerable in uremia. In order to prevent overhydration of the patient, it is necessary to limit the parenteral fluid administered daily to 1000 cc. This imposes a severe limitation on the amount of glucose which the patient can be given. Moreover, this fluid is also needed to administer the sodium lactate necessary to treat the acidosis ordinarily present. In some patients loss of fluid by continuous



gastro-intestinal aspiration can be considerable and may prove helpful in removing water or in preventing overhydration.

Some uremic patients are disoriented. Paraldehyde or barbiturates may be needed to control extreme restlessness.

If diuresis sets in, it begins by a small, but sharp, increase in volume output. The next day the output doubles or triples and the following day this volume may be doubled so that within a few days the output reaches a normal volume or commonly a polyuria is reached. For some days the urine is pale, with a low specific gravity and a urea concentration that is about equal to that of the blood. Since irrigation will have been discontinued, the blood urea or NPN; in the meantime, will rise from the reduced level produced by the irrigation. As renal function recovers, the urea output rises and finally overtakes the rate of production, so that the blood concentration curve returns toward normal.

Efficient peritoneal irrigation abstracts some 25-50 Gm. of urea daily. This is more than the normal urea production of a starving patient. As soon as the urinary urea output reaches some 10 Gm. per day in the recovery phase after acute renal failure, it can be safely assumed that the renal function will keep pace with urea production and the outlook for recovery is good. Phenolsulfonphthalein excretion and urea clearance tests at this time will show low function (20-30 per cent of normal) and the specific gravity of the urine will be between 1007 and 1010. The ileus will have largely disappeared and oral alimentation will be near normal except for occasional nausea or food intolerance. Vitamins and antibiotics will be discontinued as improvement occurs, but blood may be needed for persistent anemia.

All of the foregoing details of therapy have been applied to each patient only in the last four cases, except that one was irrigated for only 48 hours. Three of these developed peritoneal contamination, two with *E. coli* and one with *B. subtilis*. Three of the four patients survived; the fourth died of an irreversible renal injury. It appears, therefore, that even preventing contamination from the skin, air, or irrigating fluid by careful observance of all the details described, will not prevent peritonitis.

*E. coli* has been the usual pathogen responsible for peritonitis. It is possible that in the uremic patient serosal irritation by the irrigating fluid may cause transmural migration of intestinal bacteria.\* Therefore, the routine oral administration of sulfthalidine in maximal doses is used to diminish the intestinal content of *E. coli*. Penicillin is given intravenously to all patients from the outset. Streptomycin is used only after infection occurs, because of rapid development of fastness. These antibiotics did not prevent or cure *E. coli* peritonitis, even when they were also added to the irrigating fluid. Polymyxin or duomycin, when available, may prove more useful for this purpose.

The cases which follow are presented in detail for the purpose of deline-

ating the way in which the method, as previously published, was altered as a result of experience from one case to the next, until it evolved into the form now being employed.

#### CASE REPORTS

Case 5\*.—W.S. (BIH 88032): A 43-year-old man, who had been in good health, cleaned furniture with carbon tetrachloride for two hours in a warm, closed room, a week before admission. He felt "groggy" and then developed throat irritation, cough, fever, costovertebral angle and right upper quadrant pain and tenderness, subconjunctival hemorrhages, nosebleeds, occipital headache, diarrhea, increasing dyspnea, icterus and oliguria. During the three days before admission to this hospital he received 10,000 cc. of fluid and produced a total urine output of 390 cc. Generalized and pulmonary edema developed.

On admission he was acutely ill, dyspneic, vomiting, icteric, and complaining of diffuse abdominal pain. He showed orbital and conjunctival hemorrhages, an enlarged liver, and abdominal muscle spasm. Arterial pressure was 180/100 mm. Hg. The urine contained albumin and had a maximal specific gravity of 1010. The blood NPN was 105 mgm. per cent,  $\text{CO}_2$  combining capacity 47.5 vols. per cent, calcium 7.4 mg. per cent, phosphate 10.3 mg. per cent and the icteric index 32.5. Treatment for three days with concentrated glucose solution given intravenously, oxygen and penicillin was attended by steady deterioration of the patient's condition, with increasing dyspnea, tachycardia and daily urine outputs of 65 cc., 135 cc. and 300 cc. respectively. The NPN rose to 135 mg. per cent. The BUN was 76 mg. per cent. On the fourth hospital day, an inflow tube and sump drain were inserted into the peritoneal cavity under local anesthesia and irrigation was started.

The irrigating solution contained glucose in  $1\frac{1}{2}$  per cent concentration in addition to the salts of Tyrode's solution. Peritoneal irrigation was carried out for 48 hours at a flow rate of 35 cc./min. during the first day and of 25 cc./min. during the second. The urea N concentration of the outflow fluid was 42-45 mg. per cent. The total urea removed on the first day was 46 Gm. and on the second 35 Gm. The peritoneal urea clearance rate averaged 21-22 cc./min. The blood NPN after 48 hours of irrigation was lowered to 94 mgm. per cent and the blood urea N to 44 mg. per cent. The  $\text{CO}_2$  combining capacity, however, dropped to 29 vols. per cent and the blood phosphate remained elevated at 11 mg. per cent. During the two days of irrigation the urine volumes were 215 cc. and 225 cc. respectively. The urine urea content was only 75 to 80 mg. per cent and the total urinary urea excretion during the 48 hours of irrigation was 0.8 Gm.

There was a deficit of outflow ranging from .3 to 7 liters per 24 hours, which, in part, represented leakage into dressings and in part may have been due to absorption of fluid. Increasingly severe pulmonary edema and dyspnea did not respond to medication, which included oxygen, tourniquets, morphine, alkali therapy and calcium. The patient died on the sixth hospital day.

Postmortem examination\* disclosed severe pulmonary edema and confluent bronchopneumonia. The kidneys and liver were edematous and congested. There was no evidence of peritoneal infection. Microscopy showed a lower nephron nephrosis, i.e., normal glomeruli, necrobiosis and desquamation of the ascending limbs of Henle's loops and distal convoluted segments, especially at the cortico-medullary junction, where interstitial edema, lymphocytes and plasma cells were present.

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\* See reference<sup>1</sup> for cases 1-4.

*Comment.* Acute renal failure was due to carbon tetrachloride nephrosis<sup>13, 14</sup>. The peritoneal irrigation progressed with ease and efficiency, but acidosis, hyperphosphatemia and hypocalcemia were not corrected. Peritoneal infection did not occur. Pulmonary edema and confluent bronchopneumonia were the immediate cause of death. The carbon tetrachloride fumes undoubtedly produced some of the pulmonary pathology, but excessive fluid administration prior to hospital admission and the absorption of irrigating fluid from the peritoneal cavity were major contributing factors in the development of pulmonary edema.

The increase in glucose from 1.5 Gm. to 15 Gm. per liter of irrigating fluid did not prevent water absorption.

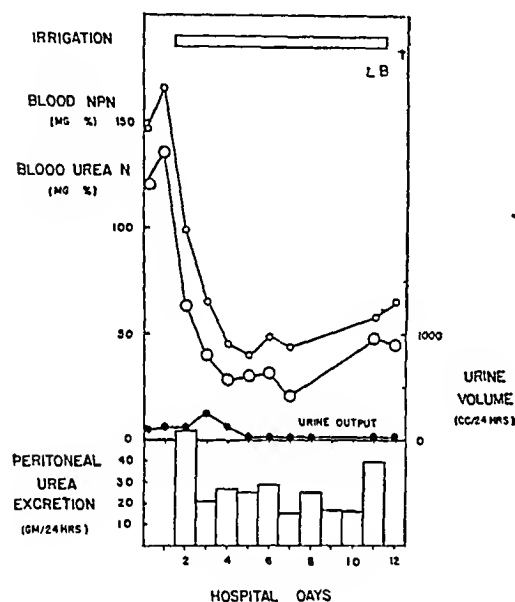


Fig. 7. Case 6.

**Case 6.—L. B. (BIH 88238):** A 55-year-old man, with rheumatic heart disease and subacute bacterial endocarditis, entered another hospital for progressive oliguria. Study there showed albumin and many red and white cells in the urine, no concentration of diodrast by the kidney and a blood NPN of 140 mg. per cent. Physical examination disclosed malnutrition, rheumatic heart disease and a blood pressure of 95/50 mm. Hg. Repeated blood cultures yielded streptococcus viridans. Three thousand cc. of 5 per cent glucose in distilled water, administered intravenously, daily for five days failed to induce diuresis. Edema of the face and legs developed and the patient became drowsy. Renal failure was believed to be due to acute glomerulonephritis. He was transferred to us for irrigation.

During the first 36 hours prior to irrigation he received 100,000 units of penicillin intramuscularly, every two hours, and 1500 cc. of 30 per cent dextrose intravenously. The daily urine output did not exceed 100 cc. The blood NPN rose to 166 mg. per cent, the BUN to 136.5 mg. per cent, the blood pressure to 150/100 mm. Hg. The CO<sub>2</sub> combining capacity was 37 vols. per cent, the blood NaCl 534 mg. per cent, calcium 7.1 mg. per cent, phosphate 11.0 mg. per cent, serum protein 6.73 Gm. per cent (albumin 2.37 Gm. and globulin 4.36 Gm. per cent). The patient became semi-comatose. Temperature and pulse rate were normal.

Continuous irrigation by an inflow tube and sump drain was started. *Tyrode's solution*, containing 2 per cent glucose was used at a rate of 35 cc. per min. The blood NPN and urea N levels returned to normal by the third day of irrigation (Fig. 7, Table I.). Concomitantly the patient became alert. A brief bout of pulmonary edema following the intravenous administration of a liter of 30 per cent glucose on the second day of irrigation was treated by tourniquets and digitalization. Some 450 Gm. of glucose was absorbed daily from the peritoneal cavity.

\* We are indebted to the Department of Pathology under the direction of *Dr. Monroe Schlesinger* for the reports of the postmortem findings.

TABLE I—Case 6

Day	Adm.	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
Peritoneal fluid:													
Urea N (mg. %)	..	57.5	19.5	24.3	22.0	23.0	17.0	21.2	..	37.5	33.8	41.8	..
Urea clearance (cc./min.)	..	..	28.0	18.0	34.0	27.0	17.0	..	..	..	..	27.0	..
Culture	..	..	..	..	..	..	..	<i>E. coli</i> <i>G + diplococci</i>	..	..	<i>B. pyocyaneus</i> <i>B. subtilis</i>	..	..
Urine:													
Urea N (mg. %)	260	250	107.5	0	0	12.5	7.5	35.0	0	..	..	32.5	15.0
Specific gravity	..	1.006	1.006	1.005	1.006	1.006	1.010	1.010	..	..	..	..	..
Reaction	..	alk.	alk.	acid	acid	alk.	acid	acid	..	..	..	..	..
Albumin	..	4+	4+	4+	4+	3+	..	3+	..	..	..	..	..
Blood:													
CO <sub>2</sub> cap. (vol. %)	37.0	37.0	26.0	25.5	22.5	26.0	41.5	40.0	..	..	..	..	36.0
Cl <sup>-</sup> (as NaCl mg. %)	534	..	630	..	780	..	790	776	..	..	..	..	776
PO <sub>4</sub> <sup>-</sup> (mg. %)	11.0	..	..	..	..	..	6.5	5.6	..	..	..	..	6.5
Ca ++ (mg. %)	7.1	..	..	..	8.0	..	..	..	..	..	..	..	..
Plasma protein (Gm. %)	6.7	..	..	..	7.4	..	..	..	..	..	..	..	..
Arterial Blood Pressure													
(mm. Hg)	$\frac{100}{50}$	$\frac{130}{80}$	$\frac{150}{100}$	$\frac{150}{100}$	$\frac{130}{60}$	$\frac{130}{70}$	$\frac{130}{80}$	$\frac{110}{70}$	$\frac{100}{70}$	$\frac{110}{60}$	$\frac{120}{60}$	..	..
Intravenous fluid:													
30% glucose in H <sub>2</sub> O (cc.)	..	1000	1021	1000	1000	..	..	..	1000	1000	1500	1000	..
Blood (cc.)	..	..	..	..	500	..	..	..	500	..	..	500	..

Acidosis increased, the  $\text{CO}_2$  combining capacity having dropped to 22 vols. per cent by the fourth day of irrigation. The irrigating fluid, therefore, was modified by adding 2.35 Gm. of sodium lactate per liter, which raised the pH of the solution to 8.3. The blood  $\text{CO}_2$  combining capacity returned to 41 vols. per cent within two days. This more alkaline solution was used thereafter in two of every three carboys of irrigating fluid. Penicillin was continued and blood and plasma given from time to time. The patient remained afebrile. He was able to eat on the fifth day of irrigation, but oliguria persisted.

On the seventh day of irrigation, culture of the peritoneal outflow fluid disclosed *E. coli* and gram positive diplococci. Thereafter, a third of a gram of streptomycin was added to each 20 liter carboy of solution and irrigation was continued. The general condition remained good for another two days, after which abdominal pain and tenderness, productive cough, fever, and a rapid pulse appeared. The patient died on the tenth day of irrigation. Blood chemical findings just before death were near the normal range. Peritoneal culture the day before death disclosed *B. pyocyaneus* and *B. subtilis*.

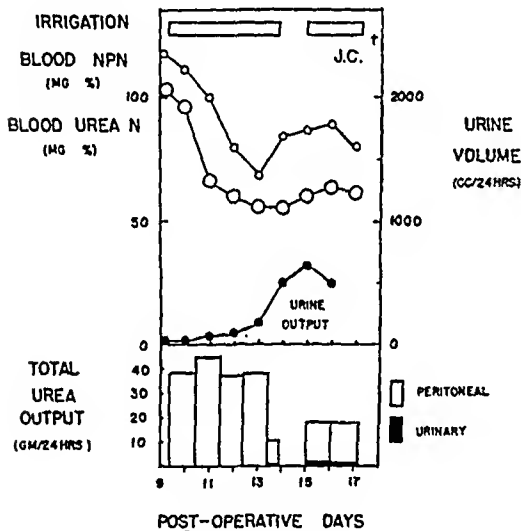


Fig. 8. Case 7.

the renal failure by continuous irrigation, ten days of which produced marked clinical improvement and restoration of the blood chemistry to near normal levels. While systemic edema, present on admission, did not increase, the bout of acute pulmonary edema following 30% glucose intravenously may have played some role in the patient's death. The addition of sodium lactate to the irrigating fluid corrected acidosis, so that intravenous alkali therapy was unnecessary. Diffuse fibrinopurulent peritonitis developed and was the immediate cause of death. The degree of renal damage suggests that spontaneous recovery from uremia was unlikely.

**Case 7.—J.C. (BH88742):** A 56-year-old man, underwent a one-stage Whipple operation for carcinoma of the ampulla of Vater and common bile duct nine days before transfer to this hospital. The patient's condition remained good for the first five postoperative days, during which time he was able to eat and walk. He then developed fever, jaundice, distention, progressive oliguria and a rising BUN. He was transferred to us on the 9th postoperative day for irrigation. On inserting the inflow tube and sump drain into the peritoneal cavity, a large volume of clear, icteric peri-

Autopsy showed mitral stenosis and insufficiency, subacute bacterial endocarditis of the mitral valve, pulmonary edema, basilar atelectasis and early diffuse fibrinopurulent peritonitis. The kidneys were swollen and congested. Microscopically they showed widespread fibrosis, epithelial proliferation, focal necrosis, and polymorphonuclear leucocytic infiltration of the glomeruli, i.e., chronic glomerulonephritis with an acute exacerbation.

**Comment.** The patient was a dubious choice for this therapy. Since the endocarditis might be expected to respond to penicillin, it was considered desirable to treat

toneal fluid was found and evacuated. Culture of the fluid, reported later, disclosed alpha streptococci and diphtheroids. *The irrigating fluid was Tyrode's solution plus 2 per cent glucose, penicillin and streptomycin. From time to time, one third of the chloride in the solution was replaced by bicarbonate or lactate to combat acidosis.* In the first three days the irrigation flow rate was 36 cc. per minute, but thereafter recurrent interference with outflow substantially reduced the average rate of flow. The blood NPN and urea N levels were substantially reduced and the blood CO<sub>2</sub> combining capacity increased to 36-48 vols. per cent, but the blood calcium remained low (see Table II and Fig. 8). After five days of irrigation, an increase in urine output from practically none to 500 cc. per day occurred.

TABLE II—Case 7

Postoperative Day	9th	10th	11th	12th	13th	14th	15th	16th	17th
Peritoneal Fluid:									
Urea (mg. %)	..	35	41	33	38	37	..	30	37
Urea Clearance (cc./min.)	..	13	19	19	22	8	..	9	11
Culture (streptococci) (diphtheroids)		E.coli							
Urine:									
Urea N. (mg. %)	..	33	..	120	158	143	133	165	168
Sp. gravity	..	1.008	1.010	1.016	1.011	1.010	..	..	..
Reaction	..	alk	alk	alk	alk	alk	..	..	..
Albumin	..	2+	0	4+	4+	4+	..	..	..
Blood:									
CO <sub>2</sub> cap. (vol %)	41	45	36	47	48	43	..	48	50
Cl <sup>-</sup> (as NaCl mg. %)	..	584	..	680	700	696	..	646	..
PO <sub>4</sub> <sup>-</sup> (mg. %)	..	5.5	..	4.5	..	..	..	5.7	..
Ca <sup>++</sup> (mg. %)	..	7.4	..	7.4	..	..	..	6.7	..
Plasma protein (Gm. %)	..	6.6	..	..	6.3	..	..	..	7.8
Hemoglobin (%)	75	68	65	64	70	..	..	..	..
Arterial B.P. (mm. Hg)	$\frac{130}{70}$	$\frac{140}{80}$	$\frac{140}{80}$	$\frac{140}{80}$	$\frac{140}{70}$	$\frac{130}{70}$	$\frac{140}{70}$	$\frac{120}{70}$	$\frac{90}{70}$

The clinical condition—fever, tachycardia, jaundice, hallucinations, and delirium—worsened. A large quantity of cloudy fluid containing pancreatic amylase oozed from the operative incision for several days. Intestinal distention necessitated intubation, which yielded 2000-4000 cc. of fluid per day. Penicillin (1-2 million units) and streptomycin (2-4 Gm.) were given intramuscularly daily and transfusions for anemia were given repeatedly. Streptococci were not found again in the peritoneal fluid, but *E. coli* appeared in the outflow fluid on the third day of irrigation.

A comparison of outflow with inflow volumes indicated no significant retention of irrigating fluid and no generalized edema developed. But pulmonary edema appeared abruptly on the eighteenth postoperative day, when the patient died.

Postmortem examination disclosed confluent bronchopneumonia, marked peripancreatic fat necrosis and hemorrhage, multilocular purulent peritonitis and obstruction at the biliary anastomosis. The histologic examination of the kidneys disclosed little damage. A mild degree of focal "lower nephron" nephrosis, in the healing stage, was found.

*Comment.* Renal failure consequent to the development of peritonitis is a familiar experience. The existence of peritonitis was not realized when

the irrigation was started, but became obvious later. Irrigation was continued in order to observe its effectiveness in the circumstances. The blood nitrogenous levels responded in spite of recurrent blocking of outflow, which was possibly due to the peritonitis. It is difficult to assess the influence of the

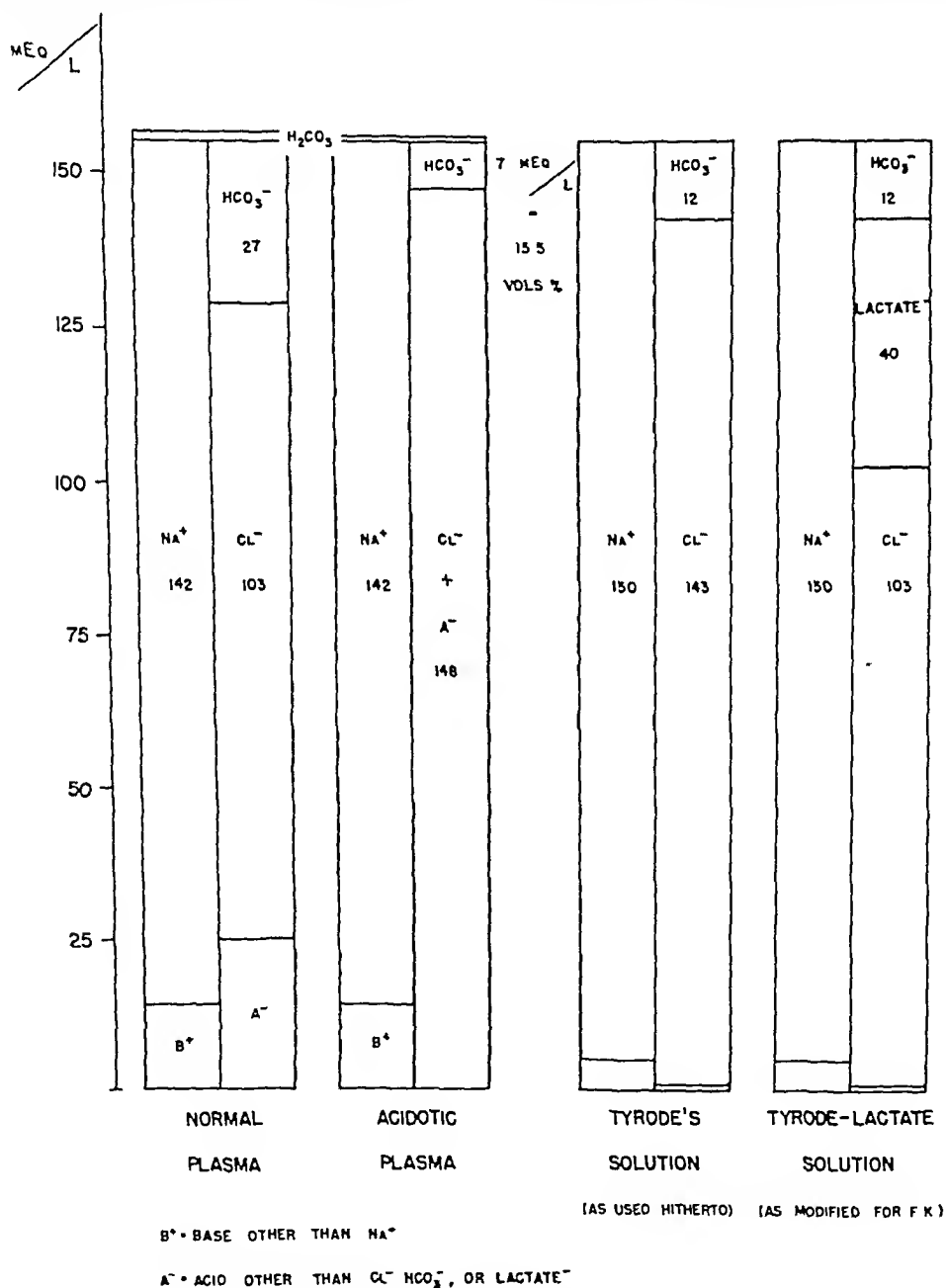


Fig. 9. — Diagram (modeled after Gamble) of acid-base equivalence of modified irrigating solution used in case 8.

irrigation procedure on the course or spread of the peritonitis. On the basis of our experience with irrigation after peritonitis has set in, we are inclined to believe that it may have done more harm than good.

In this patient, as in the last, edema did not occur. The substitution of

bicarbonate or lactate for one-third of the ionic equivalent of chloride in the irrigating solution resulted in effective control of acidosis.

**Case 8.**—F.K. (BIH 91435): A 44-year-old chronic alcoholic, was admitted to another hospital complaining of progressive reduction in urinary output of three weeks' duration, associated with a dull, persistent ache in both flanks and mid-back. One week before admission he stopped working because of anorexia and extreme fatigability. He was then able to void only a few cc. of bloody urine daily and noticed puffiness of the eyelids. On admission the lower eyelids were ecchymotic, the liver edge was three finger breadths below the right costal margin, the blood pressure was 145/85 mm. Hg., the red cell count 3.7 million and the hemoglobin 12 Gm. per cent. The urine was alkaline and contained albumin, glucose, red and white cells. Cystoscopy and retrograde pyelography revealed no abnormality. The blood NPN levels were 138, 165, and 150 mg. per cent, the CO<sub>2</sub> combining capacity 32, 29, and 24 vols. per cent respectively, on three succeeding days after admission. Bilateral renal decapsulation was done the day following admission. No gross abnormality of either kidney was noted. During this three-day period the patient voided a total of 110 cc. of urine and received a total of 13 liters of fluid.

On transfer to us for peritoneal irrigation the patient was drowsy, and respiration was acidotic. There were moist rales at the right lung base, but no peripheral edema. Both flank incisions were healing well. The blood pressure was 145/80 mm. Hg. The blood NPN was 124 mg. per cent, BUN 109 mg. per cent, CO<sub>2</sub> combining capacity 25.5 vols. per cent and chlorides 458 mg. per cent. No urine could be obtained. Five hundred cc. of 30 per cent glucose in water were given intravenously for starvation acidosis.

On the following day, continuous peritoneal lavage, through an inflow tube and sump drain was instituted. A modified Tyrode's solution\* containing 2 per cent glucose was used (Fig. 9).

The pH of this solution after autoclaving was 7.9.

Because of incipient pulmonary edema, no fluid was given intravenously at first. The irrigating fluid was relied upon to provide glucose. Penicillin, streptomycin, and the water-soluble vitamins were given intramuscularly. Irrigation was continued at flow rates averaging 31, 36, 38, 23, 23, and 26 cc. per minute on the six successive days respectively (see Table 3 and Fig. 10). During the first three days the patient showed progressive subjective and objective improvement. In this period the peritoneal urea clearance varied from 8.5 to 15.6 cc. per minute, and the blood NPN and BUN fell to 68 and 45 mg. per cent respectively. The blood CO<sub>2</sub> combining power dropped steadily to 15.5 vols. per cent in spite of sodium lactate in the irrigating fluid, and the absorption of some 250 Gm. of glucose per day. Five-hundred cc. of one-sixth or one-third molar solution of sodium lactate, therefore, was given intravenously each day and the blood CO<sub>2</sub> combining capacity returned to normal. The daily urine output, which was never greater than 150 cc., eventually declined toward zero. The daily blood pressure varied from 150 to 170 mm. Hg. systolic and 80 to 100 mm. Hg. diastolic.

	<i>Gm. per liter</i>
NaCl	5.7
NaHCO <sub>3</sub>	1.0
Na lactate	4.5
KCL	0.2
CaCl <sub>2</sub>	0.1
NaH <sub>2</sub> PO <sub>4</sub>	0.05
MgCl <sub>2</sub> .6H <sub>2</sub> O	0.22
Dextrose	20.0

\*Composition of modified Tyrode's solution



Mild abdominal distention was not relieved by tube suction. Thereafter, peritoneal lavage became progressively less efficient and the blood NPN and urea N levels slowly increased. On the eighth day local signs of peritonitis appeared. The outflow fluid contained many polymorphonuclear leucocytes and gram negative bacilli, including *E. coli*, *B. aerogenes* and Friedlander's bacillus. He expired that evening.

Postmortem examination disclosed diffuse fibrino-purulent peritonitis. The kidneys were large and the perirenal fat was edematous, indurated and hemorrhagic. Most of the true renal capsule had been removed. Microscopic examination disclosed a tubular nephritis. The great majority of the tubules showed swelling, disintegration, necrobiosis, and desquamation in the proximal and distal convoluted portions and in the limbs of Henle's loops, with evidence of early regeneration, particularly in the proximal convoluted tubules. There was considerable interstitial edema.

TABLE III—Case 8

Hospital day	Adm.	1st	2nd	3rd	4th	5th	6th
<b>Peritoneal fluid:</b>							
Urea N (mg. %)	..	47	19	12	13	12	15
Urea clearance (cc. min.)	..	16	12	9	4	5	6
Culture	..	..	..	..	..	<i>E. coli</i> Friedlander's bacillus <i>B. aerogenes</i>	..
<b>Urine:</b>							
Urea N (mg. %)	..	38	86	112	107	198	..
Urea clearance (cc. min.)	.....	negligible.....					
Specific gravity	..	1010	1002	1007	1008	..	..
Reaction	..	alk.	alk.	acid	acid	..	..
Albumin	..	4+	3+	2+	3+	..	..
<b>Blood:</b>							
CO <sub>2</sub> cap. (vol. %)	26	21	16	23	36	..	48
Cl <sup>-</sup> (as NaCl mg. %)	458	564	..	..	..	..	530
<b>Fluid balance:</b>							
Peritoneal inflow (L.)	..	47	52.5	55.2	36	33.5	38
Peritoneal outflow (L.)	..	43	52	53	26	36	40
Lactate (cc.)	..	500(M/6)	500(M/3)	500(M/6)	..	..	..
Oral	..	2190	1505	1510	2000	1700	800
Gastric drainage (cc.)	..	..	..	100	1500	1200	900
Glucose retained from irrigating fluid (Gm. /day)	..	206	182	185	109	309	250

*Comment.* The cause of the loss of renal function was not known. Autopsy showed acute diffuse tubular damage. Although histologic evidence of early regeneration was seen, there was no recovery of renal function and no evidence that decapsulation had produced benefit.

For some 48 hours the irrigation accomplished its purpose, except for failure to control acidosis in spite of the presence of lactate in the irrigating solution. The acidosis was readily corrected by intravenous sodium lactate. Edema did not develop. The treatment failed and the patient died because of peritonitis due to gram negative bacilli. The efficiency of irrigation decreased after the first two days, possibly because of peritonitis, which probably developed two days before it was recognized clinically.

Although sodium lactate in the irrigating solution was effective for control of acidosis in two of the three patients in whom it was used, all three developed peritonitis. This may have been due to the prolonged period of irrigation, but the possibility that the increased alkalinity of the solution may have irritated the peritoneum sufficiently to reduce its resistance to bacterial growth or to encourage migration of bacteria through the wall of the intestine, led us to abandon the use of sodium lactate in the solution.

The formula for subsequent clinical use then determined upon was modified Tyrode's solution with gelatin and glucose for the purpose of preventing fluid absorption. It was felt that further increase in glucose alone for this purpose, might prove too irritating. Because the gravity flow of the solution containing gelatine through the diatomaceous bacterial filter is too slow, the filter thenceforth was removed from the inflow circuit.

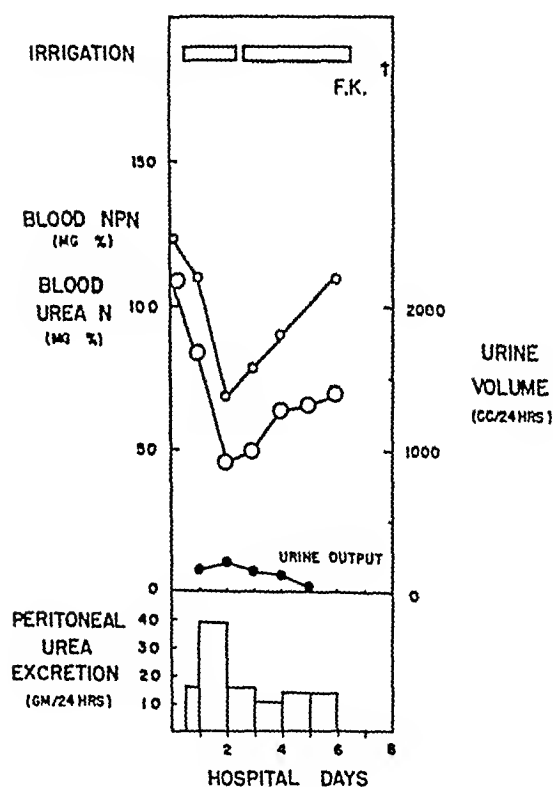


Fig. 10. Case 8.

Case 9.—G.H. (BIH 91590): A 53-year-old man underwent perineal prostatectomy at another hospital. After 48 hours of normal urine output, acute renal failure set in following a severe reaction to the intravenous infusion of 200 cc. of 5% glucose in saline. The febrile reaction was followed by wound hemorrhage and shock. Acidosis was prevented by the intravenous administration of sodium bicarbonate. Severe oliguria persisted for 10 days. The patient was then sent to us for peritoneal irrigation. He was in advanced uremia, with edema from overhydration. *Peritoneal irrigation was carried out with a modified Tyrode's solution containing 1 per cent gelatin and 2 per cent glucose.* The patient died 31 hours after irrigation was started. During this time 18.5 Gm. of urea in the 43 liters of outflow fluid was recovered. The outflow fluid remained sterile. Postmortem examination disclosed intestinal distention, but no peritoneal infection. The kidneys showed a typical lower nephron nephrosis, with healing in progress.

*Comment.* The etiology of the kidney injury is obscure. A pyrogenic and apparently hemolytic reaction accompanied the intravenous administration of glucose in saline and was followed by a prolonged period of hemorrhagic shock. No incompatible blood was given. There was no recovery of renal function in spite of the histologic evidence of healing.

Peritoneal irrigation was initiated when the patient was moribund. Little benefit could have been expected and none was observed. The presence of gelatin (1 per cent) and glucose (2 per cent) was effective in preventing the

absorption of water from the peritoneum. Outflow equalled inflow volume, and the patient's edema did not increase. No peritoneal infection occurred.

**Case 10.**—E.M. (BIH 91718): A 43-year-old male, was admitted to a neighboring hospital complaining of bilateral low-back pain of eight weeks' duration, progressive oliguria of three weeks' duration, and anorexia, nausea and vomiting for four days. One week prior to entry he experienced a severe chill. On admission, the blood pressure was 140/90 and the pulse 68. There were moist rales at both lung bases, but no other positive physical findings. Laboratory data were normal except for a blood NPN of 187 mg. per cent, a  $\text{CO}_2$  of 36 vols. per cent. No urine was found on catheterization of the bladder. Retrograde pyelography revealed no abnormality of bladder, ureters or renal pelves. High spinal anesthesia failed to induce urinary flow. He was transferred to us for peritoneal irrigation.

There were fine moist rales in the lower lung fields. The abdomen was distended and tympanitic. The right Babinski sign was positive, there was bilateral ankle clonus and involuntary muscle twitchings. Vomiting was frequent. The blood pressure was 150/85 mm. Hg. Laboratory data showed a RBC 3,870,000; Hgb. 13.6 Gm.; WBC 19,500; NPN 216 mg. per cent; BUN 164 mg. per cent;  $\text{CO}_2$  combining power 46.5 per cent. There was no urine.

Three hours following admission *continuous irrigation through an inflow tube and sump drain was started, using a modified Tyrode's solution\** flowing at an average rate of 24 cc. per minute for two and one-half days. Water-soluble vitamins and penicillin were given intramuscularly and sulfathalidine orally. On the second day of irrigation the patient was given 150 grams of glucose intravenously in a total of 1700 cc. of water. The chest x-ray film showed pulmonary congestion and bilateral hydrothorax.

The blood urea clearance by peritoneal irrigation varied from 12.3 to 19.0 cc. per minute during this period and the urea excretion averaged 40 grams per day. The blood NPN and urea N declined, but the  $\text{CO}_2$  combining power

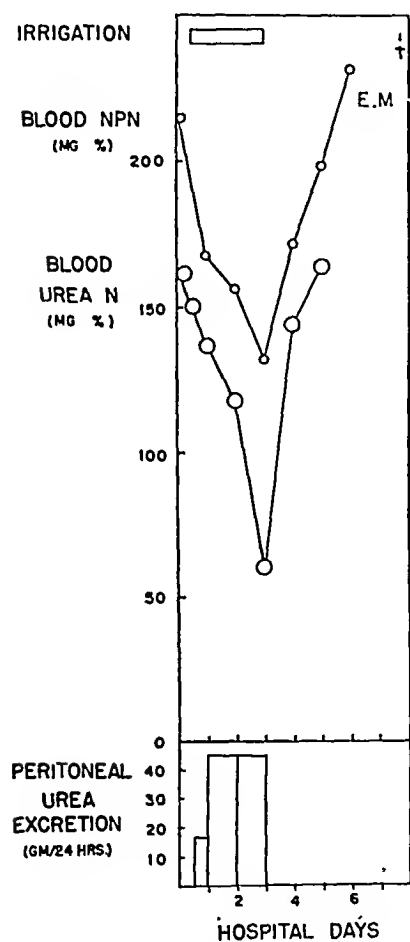


Fig. 11. Case 10.

remain essentially unchanged (Fig. 11 and Table 4).

	Gm. per liter
gelatin	10.0
glucose	5.0
$\text{NaHCO}_3$	2.25
$\text{NaCl}$	6.25
$\text{KCl}$	0.2
$\text{CaCl}_2$ (anhyd)	0.1
$\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$	0.2
$\text{NaH}_2\text{PO}_4$	0.05

\*Composition of irrigating solution:

## ACUTE RENAL FAILURE

Substantial subjective improvement was evident, but the daily urine output remained less than 30 cc. Sixty hours after irrigation was started the peritoneal drainage fluid was cloudy and yielded a growth of staphylococcus albus and diphtheroids, which were also cultured from the wounds the next day. Irrigation was immediately discontinued.

Thereafter, the blood NPN and the clinical evidence of uremia increased. Abdominal distention required intubation. A peritoneal tap two days and again four days after cessation of irrigation, yielded a pure culture of *E. coli*. Streptomycin therapy was given (6 gm. in 48 hours) but the patient grew rapidly worse, developed mild generalized and pulmonary edema, became comatose and died four days after irrigation was discontinued. There was no urine output in the last 4 days of life.

Postmortem examination revealed yellow, cloudy peritoneal fluid and small flakes of purulent material covering the serosal surfaces of the upper abdominal viscera. There was mild edema of the lower lobes of the lungs. Both kidneys were markedly enlarged, swollen and deeply congested, weighing 260 Gm. each. Microscopy showed

TABLE IV—Case 10

Hospital day	Adm.	1st	2nd	3rd	4th	5th	6th	7th
<b>Peritoneal fluid:</b>								
Urea N (mg. %)	62.7	99.7	72.6	..	..	..	..	..
Urea clearance (cc./ min.)	12.3	19.0	12.7	..	..	..	..	..
Culture		sterile		staph. albus diphtheroids		<i>E. coli</i>		<i>E. coli</i>
<b>Urine:</b>								
Urea N (mg. %)	..	232	..	..	..	..	..	..
Reaction	..	alk.	..	..	..	..	..	..
Albumin	..	4+	..	..	..	..	..	..
Culture	..	<i>E. coli</i>	..	..	..	..	..	..
<b>Blood:</b>								
CO <sub>2</sub> cap. (vol. %)	46.5	38.5	38.5	40.5	42.0	29.0	51.0	..
Cl <sup>-</sup> (as NaCl mg. %)	..	..	560	..	..	..	..	..
Plasma protein (Gm. %)	..	..	..	..	5.8	..	..	..
Hemoglobin (%)	..	76	94	100	..	..	..	..
<b>Arterial Blood Pressure</b>								
(mm. Hg)	$\frac{150}{85}$	$\frac{130}{75}$	$\frac{120}{80}$	$\frac{130}{90}$	$\frac{120}{60}$	$\frac{105}{60}$	..	..

crescentic epithelial proliferation, adhesions, splitting, thickening and fusion of the capillary basement membrane, or complete fibrosis of the great majority of the glomeruli. In many, necrosis, hemorrhage and an exudate of polymorphonuclear leucocytes were present. There was a diffuse interstitial infiltration of lymphocytes and plasma cells. No vascular lesions were found. Diagnosis: Chronic proliferative and acute exudative glomerulonephritis.

*Comment.* Although a presumptive diagnosis of glomerulonephritis was made on admission, the uncertainty of the diagnosis and, therefore, the possibility of recovery of kidney function led to a trial of peritoneal irrigation, which achieved a blood urea clearance of 12-19 cc/min., reducing blood nitrogenous levels, eliminating 40-50 grams of urea per day, and producing subjective improvement. One per cent gelatin and one-half per cent dextrose were used in the irrigating fluid. The outflow fluid volume was 0.6 to 6.0 liters less than the inflow per 24 hours.

Although on one occasion the peritoneal outflow fluid contained the same organisms found in the wound (staphylococcus albus and diphtheroids), the organism responsible for the peritonitis was *E. coli*, in pure culture. Streptomycin therapy produced no detectable benefit.

Changes in technic were then designed to exclude as rigidly as possible the introduction of bacteria *via* the irrigating fluid, even though the repeated finding of *E. coli* as the predominant infecting organism suggested that transmural migration of intestinal organisms was the likely source of the peritonitis: (1) The open-top sump drain was redesigned. A closed top to

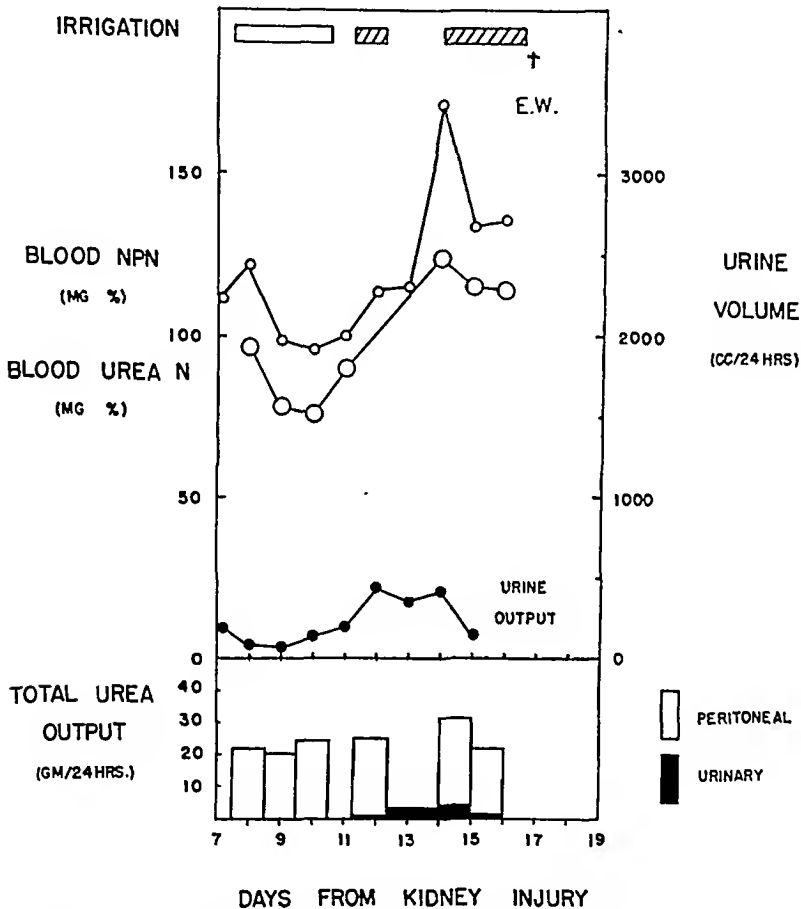


Fig. 12. Case 11.—(Open bar indicates continuous irrigation; cross-hatched bar indicates intermittent irrigation.)

prevent the escape of fluid into the dressings and a side-arm for the inlet of filtered air was provided.\* (2) Another change in technic introduced at this time was the preparation of the irrigating fluid by adding all its constituents at once to cooled freshly distilled water and sterilizing by Berkefeld filtration rather than by heat. This was tried in the following case, but was later aban-

\* The principle of a sump drain is to maintain atmospheric pressure in the sump cylinder so as to avoid drawing surrounding tissues into the drain. Structures were not drawn into the holes of the outside cylinder in spite of the slight negative pressure.

done because of the lack of proper apparatus to filter safely large volumes of fluid under pressure. The technic now in use for preparing the solution was, then devised and is described in the preceding section of this paper.

**Case 11.—E.W. (BIH 92825):** A 32-year-old woman, who had received sulfadiazine for pneumonia four years earlier, was given 0.5 Gm. of sulfadiazine every four hours for three days for pain and swelling of the left cheek, associated with a slight sore throat. At the end of this period she noticed edema of the face and eyes, moderate pain and tenderness in the midback and inability to void more than very small amounts of urine. A catheter specimen of urine contained albumin (4+), many granular casts and red and white blood cells. The blood pressure was 130/90 mm. Hg. and the blood NPN was 122 mg. per cent. Catheterization of the ureters revealed no obstruction. During the subsequent four days treatment consisted in forced fluids, hypertonic dextrose, magnesium sulfate, penicillin intravenously and diathermy to the renal area. The urine output averaged 100 cc. per day. Edema increased; abdominal distention and cerebral depression appeared. She was transferred to this hospital for peritoneal irrigation after seven days of oliguria.

On admission the patient was drowsy; her color was ashen gray, with moderate cyanosis of the lips and finger tips. There was edema of the face, ankles and lower back. There was dullness to percussion over the right lung base posteriorly. The abdomen was distended with fluid. A definite Chvostek sign was elicited.

A stainless steel inflow tube and a closed-top outflow sump (Fig. 3) were inserted into the peritoneal cavity. Continuous irrigations was started with a modified Tyrode's solution (Solution I\*) containing 1 per cent glucose, one-half per cent gelatin, heparin and penicillin.

Streptomycin for *E. coli* urinary infection, water-soluble vitamins, and penicillin were given parenterally. Several whole blood transfusions and a daily slow intravenous drip of 30 per cent glucose in 500 cc. of water were given. The stomach was intubated and calcium gluconate, concentrated glucose and sodium lactate were introduced through this tube. The tube could not be made to pass beyond the pylorus.

After three days of continuous irrigation with an average of 28 liters of fluid daily, and with the extraction of 20 Gm. of urea per day, there was definite clinical improvement (Fig. 12 and Table V). The patient became alert, well-oriented, and active. The daily urine volume did not exceed 200 cc. Edema decreased markedly. But increasing abdominal distention, fever and tachycardia led to discontinuing the irrigation. It was resumed 18 hours later. Phosphate was omitted from the solution (Solution II — see above), which was now introduced and withdrawn intermittently. A liter of fluid was allowed to dialyze for 45 minutes and then was removed by suction.

*Solution I (sterilized by Berkefeld filtration)		Solution II (sterilized by autoclaving)	
	Gm. per liter		Gm. per liter
NaCl	7.25		7.25
KCl	0.2		0.2
CaCl <sub>2</sub> (anhyd.)	0.1		0.1
MgCl <sub>2</sub> ·6H <sub>2</sub> O	0.2		0.2
NaH <sub>2</sub> PO <sub>4</sub>	0.05		0
NaHCO <sub>3</sub>	1.5		1.5
Dextrose	10.0		10.0
Gelatin	5.0		5.0
Final pH 7.45		Final pH 8.1 — 8.5	

TABLE V—Case 11

Day (from kidney injury)	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th
<b>Peritoneal fluid:</b>										
Urea N (mg. %)	36.3	30.4	42.9	56.5	..	..	..	39.1	85.8	85.8
Urea clearance (cc./min.)	8.0	8.4	10.3	6.8	..	..	..	5.7	11.0	11.0
Culture	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	<i>E. coli</i>
<b>Urine:</b>										
Urea N (mg. %)	71	207	194	310	280	372	507	429	528	..
Specific gravity	..	1.010	1.021	1.011	1.010	..	1.012	..	1.013	..
Reaction	alk.	alk.	acid	acid	acid	..	acid	..	acid	..
Albumin	4+	4+	4+	4+	4+	..	4+	..	3+	..
Cells	WBC	WBC	WBC	WBC	WBC	..	WBC	..	WBC	..
	RBC	RBC	RBC	RBC	RBC	..	RBC	..	RBC	..
Culture	<i>B. pyocyaneus</i>	<i>E. coli</i>		<i>B. pyocyaneus</i>			<i>B. pyocyaneus</i>			<i>B. pyocyaneus</i>
	<i>E. coli</i>									
<b>Blood:</b>										
CO <sub>2</sub> cap. (vol. %)	..	35.0	53.0	44.5	38.5	..	57.0	54.0	38.5	58.5
Cl <sup>-</sup> (as NaCl mg. %)	458	..	558	580	544	..	..	600	..	..
PO <sub>4</sub> <sup>-</sup> (mg. %)	..	11.4	..	10.7	10.0	..	..	8.9	..	..
Ca <sup>++</sup> (mg. %)	..	6.9	..	7.4	7.7	..	..	6.9	..	..
Plasma protein (Gm. %)	4.9	5.6	..	5.2	5.2	..	..	5.1	..	..
<b>Arterial Blood Pressure</b>										
(mm. Hg)	..	120 60	120 60	170 110	150 90	..	..	150 100	120 70	..
<b>Fluid exchange:</b>										
Peritoneal inflow (L.)	37.0	31.7	28.0	25.2	..	..	..	17.5	7.2	7.2
Peritoneal outflow (L.)	29.0	32.7	24.0	23.0	..	..	..	15.0	6.5	6.5
Blood transfusion (cc.)	..	..	..	500	..	..	500	500	..	500

The abdomen became so severely distended by the sixth hospital day that the fluid introduced produced marked respiratory distress. Irrigation was discontinued and the tubes were removed. All measures for relief of distention failed. The patient became manic and disoriented. An enterostomy tube was placed in a loop of small bowel. Peritoneal fluid taken for culture during this procedure was sterile. The next day (eighth hospital day) stupor, dyspnea, tachycardia and a blood NPN of 172 mg. per cent made it seem that, although urine output was increasing, adequate renal function would not occur soon enough to prevent death. A sump drain was re-inserted in the left lower abdomen under local anesthesia and intermittent irrigation was instituted, using the sump for both inflow and outflow. For some 30 hours there was progressive improvement in clinical and laboratory findings. The patient again became alert and co-operative. But *E. coli* was found in pure culture in the outflow fluid during the next two days. Acute pulmonary edema developed on the ninth hospital day. It subsided, but coma and decline in urine output developed and death followed in the tenth hospital day, 17 days after the original renal shutdown.

Postmortem examination revealed cerebral edema, congestion of the middle and lower lobes of the right lung and fibrinopurulent pelvic peritonitis. The kidneys were swollen and congested. Renal microscopy showed a lower nephron nephrosis, i.e., normal glomeruli, necrosis and hemorrhage of the lower tubular segments, which contained spherulo-radiate crystals, refractile to polarized light and resembling sulfonamide crystals. An interstitial exudate, most pronounced at the cortico-medullary junction, contained lymphocytes and plasma cells.

*Comment.* The apparent cause of the renal shutdown in this instance was sulfonamide hypersensitivity, produced by prior administration. The blood urea clearance achieved by peritoneal irrigation was not great enough to produce a substantial decline in blood NPN or urea N concentrations, but a large amount of urea was removed. Improvement in the uremic state resulted. Since this patient came to us considerably overhydrated, intravenous therapy for starvation acidosis and hypocalcemia was avoided. Intestinal distention was probably aggravated by the hypertonic glucose fed *via* the stomach tube. It is doubtful whether the enterostomy, though ill-advised, was responsible for the peritonitis, since the inflammatory reaction was confined to the pelvis and the enterostomy area was free of infection.

After this experience it was decided that the low blood calcium and the high blood phosphate should be treated not only by omitting phosphate but by increasing calcium in the irrigating fluid.

It was also decided at this time that the rigid sump drain was unsatisfactory, (1) because it was still possible for fluid to pass back and forth from the peritoneal cavity to the skin along the *outside* of the drain cylinder, and (2) because the tip of the drain could not be kept at the bottom of the pelvic cul-de-sac, which is necessary if a stagnant puddle which permits absorption of water and facilitates infection from contaminating organisms, is to be avoided. Consequently, the sump drain was shortened so as to form an aspirating tip to a flexible tube, which would be passed through the abdominal wall at staggered levels and would emerge from the abdomen well above the intraperitoneal fluid level, there to be attached to a closed system for inter-



mittent or continuous irrigation with the assurance of complete aspiration of the fluid, and without the possibility of ebb and flow between the skin and the peritoneal cavity.

**Case 12.—E.P. (BIH 93042):** A 36-year-old housewife (blood group O) received 500 cc. of incompatible blood (group A) after operation for a right tubal pregnancy at another hospital. During the transfusion a chill was followed by shock. Further transfusions (correctly matched) were given. Urine output decreased from 120 cc. on the first post-operative day to 0 cc. on the fifth, with progressive daily increase in blood NPN, which reached 140 mg. per cent on the fifth post-operative day, when she was transferred to this hospital.

On admission the patient was cyanotic, drowsy and responded only by feeble head movements. Respiration was rapid and shallow. There was dullness, bronchial breathing and a few crepitant rales at the right lung base posteriorly. The abdomen was diffusely distended, tympanitic and silent. There was a vertical suprapubic wound with skin clips *in situ*, draining blood and showing hemorrhagic extravasation. There was pitting edema of the lower back, thighs and ankles. Both optic disc margins were slightly blurred. The blood urea N was 138 mg. per cent, sodium chloride 492 mg. per cent, CO<sub>2</sub> combining capacity 55 vols. per cent, icteric index 13, calcium 5.7 mg. per cent, phosphate 9.0 mg. per cent and total protein 6.0 Gm. per cent. The Chvostek and Trousseau signs were negative.

A Miller-Abbott tube was passed beyond the pylorus, oxygen was given by mask and the intramuscular administration of penicillin and water-soluble vitamins was started.

The following morning the patient's color was better and abdominal distention was less. The chest signs were unchanged. In view of the duration and severity of the uremic state it was considered necessary to institute peritoneal irrigation without further delay. *Because of the condition of the incision and the inflammatory reaction of the peritoneum, intermittent filling and emptying of the peritoneal cavity was attempted through a large bore needle*, which was withdrawn after each filling and emptying. Approximately 2000 cc. of solution\*, an arbitrary amount determined by the patient's tolerance, was introduced at each filling, allowed to remain for three hours, after which aspiration was undertaken. Multiple punctures in a variety of sites were required to withdraw the fluid, and only 1400 cc. and 1350 cc. of fluid respectively were recovered after the first two instillations. During this period the patient received a very slow (six-hour) intravenous infusion of 30 per cent glucose in 500 cc. of water. Soon after the third peritoneal filling (1500 cc.) the patient suddenly became deeply cyanotic and markedly dyspneic, with associated tachycardia, restlessness and apprehension. Chest signs, confirmed by x-ray, were consistent with massive pulmonary edema. Paracentesis did not remove a significant amount of fluid and the operative wound had now separated widely, down to the deep fascia. Because of the patient's extremely precarious condition, therapy was limited to snug taping of the lower abdomen.

	Gm.
NaCl	7.4
KCl	0.2
CaCl <sub>2</sub>	0.2
MgCl <sub>2</sub> ·6H <sub>2</sub> O	0.22
NaHCO <sub>3</sub>	1.0
dextrose	5.0
gelatin	10.0
pH 7.1 (after autoclaving)	

\*Composition of irrigating solution (per liter)

Pulmonary edema was treated by oxygen under positive pressure, morphine and a sharply upright position of the patient in bed. The following morning respiration was slightly less labored and was improved by a right thoracentesis, yielding 500 cc. of clear yellow fluid. Diffuse coarse pulmonary rales persisted. The abdomen was softer, apparently due to absorption of retained peritoneal fluid.

The fluid retained in the peritoneal cavity, as shown by the deficit in the fluid withdrawn, totaled 2750 cc. in the 7 hour period of intermittent irrigation. The peritoneal fluid removed had a urea concentration equal to that of the blood, so that in all 3.8 Gm. of urea were removed (blood urea clearance 8.0 cc. per minute). No improvement in blood nitrogen levels was accomplished and the CO<sub>2</sub> combining capacity dropped to 43 vols. per cent.

For a day and a half following the episode of pulmonary edema no fluid was given except for the oral administration of 160 cc. of normal sodium lactate. During this period the patient's color improved, respiration became less labored and the lung fields became clearer, though scattered moist rales and dullness at both bases persisted. Peripheral edema increased. Fever (103.8°) at the end of this period was attributed to pulmonary infection. Intramuscular streptomycin (4 Gm. daily) was started and penicillin was increased to 250,000 units every four hours.

By the afternoon of this, the eighth postoperative day, the patient showed signs of marked uremic intoxication. She was semi-comatose. There were frequent tetanic movements of the extremities. The blood NPN was 182 mg. per cent, urea N 163 mg. per cent and the CO<sub>2</sub> combining capacity 37.5 vols. per cent.

*Intermittent irrigation with the single flexible sump drain was started.* Five hundred cc. of solution was introduced, allowed to equilibrate for 15 minutes, then removed by gentle suction, and replaced by fresh solution. The entire cycle required approximately thirty minutes. The overall flow rate averaged 21 cc. per minute. After seven hours of irrigation the patient regained consciousness and recognized people in the room. The irrigation was continued for forty-four hours, during which the inflow volume totaled 57 liters and the outflow 56 liters. In the first 26-hour period the urea N content of the outflow fluid was 95 mg. per cent (blood urea clearance, 12 cc. per minute) and 61 Gm. of urea were removed. The blood NPN fell to 160 mg. per cent, but the CO<sub>2</sub> combining capacity dropped to 25 vols. per cent and the venous blood pH was found to be 7.1. Sodium lactate (250 cc. of N/6 solution) and 500 cc. of blood were given intravenously. The subcutaneous edema increased but the lungs were now entirely clear. In the next eighteen hours, the urea N concentration in the outflow fluid was 54 mg. per cent (blood urea clearance 8.2 cc. per minute) and 26 Gm. of urea were removed.

The clinical state deteriorated. In spite of the rapid administration of 1500 cc. of whole blood and 1,000 cc. of plasma and the slow infusion of 20 per cent glucose, the patient died in shock and coma on the tenth postoperative day, when the blood NPN was 152 mg. per cent and CO<sub>2</sub> combining capacity 40 vols. per cent. The peritoneal outflow fluid remained sterile throughout the period of irrigation. The urine output never exceeded 60 cc. daily.

Postmortem examination revealed no evidence of peritoneal irritation, except for a small fibrinous exudate on a loop of small bowel in the vicinity of the sump drain. The lungs were edematous. This probably developed terminally as a result of the large amount of fluid given in the effort to combat shock. The brain, too, was slightly edematous. The kidneys were slightly swollen and engorged on cut section. Microscopy showed a lower nephron nephrosis, i.e., the glomerular tuft was within normal limits; the capsular space was dilated and contained abundant albuminous debris; and the tubules showed necrosis and desquamation of the epithelium in the lower segment.

A majority of the tubules contained freshly extravasated blood and rather large heme pigment casts. The tubules contained spheruloradiate crystals, which were refractile under polarized light and which resembled sulfonamide crystals.

*Comment.* This patient presented a typical syndrome of severe renal injury due to incompatible blood. No recovery of renal function was observed in the ten days she survived. Time was lost in an ineffective effort to accomplish dialysis by peritoneal filling and emptying *via* needle punctures. The absorption of a large quantity of fluid which could not be recovered by aspiration from the peritoneal cavity produced pulmonary edema and clearly demonstrated the inadequacy and the danger of such a technique for dialysis. The sump drain functioned smoothly and with excellent efficiency until shock developed, probably because treatment of the uremia was begun too late.

**Case 13.—B.C. (BIH 93563):** A 38-year-old bartender, entered a neighboring hospital for pneumonia and delirium tremens. Sulfadiazine (22 Gm.) and sodium bicarbonate (22 Gm.) were given in the first three days. He also received penicillin, paraldehyde, sodium phenobarbital, sodium bromide, demerol and hyoscine. Anuria occurred on the third day and sulfadiazine was omitted. No obstruction of the ureters was demonstrated.

After three days of anuria he was transferred to this hospital. He was cyanotic, orthopneic, disoriented and extremely irritable. His breath had a sweetish odor. There was limited expansion of the right side of the chest, with signs of consolidation in the right upper lobe and fine moist rales at both bases. The abdomen was distended. The skin showed a generalized maculopapular rash.

Temperature on admission was 100°F., pulse 100, respirations 30, blood pressure 150/100 mm. Hg. There was no urine. RBC was 3.43 million, Hg. 85%, and WBC 19,000. Blood NPN was 206 mg. per cent, BUN 170 mg. per cent and NaCl 464 mg. per cent. X-ray examination revealed haziness of the upper two thirds of the right lung and of the mid-lung field on the left and elevation of the right diaphragm. Abdominal films showed gaseous distention of the small intestine and ascites.

Penicillin and paraldehyde were given parenterally. Oxygen was given by mask and tube suction was instituted. Whiskey orally and sulfathalidine by tube were administered. The following day the patient received 500 cc. of blood, followed by 1,000 cc. of 10 per cent glucose in saline intravenously. A catheter recovered 100 cc. of grossly bloody urine, which was alkaline, with a specific gravity of 1018, and contained albumin and a sediment packed with erythrocytes. *E. coli*, enterococci, pyocyanus and proteus were grown on culture of the urine. The rectal temperature ranged from 101° to 104° and the pulse rate from 100 to 120.

On the third hospital day the blood NPN was 228 mg. per cent, blood urea N 203 mg. per cent, CO<sub>2</sub> combining power 36 vol. per cent, NaCl 496 mg. per cent and sulfadiazine level 11.4 mg. per cent. The RBC had increased to 5.1 million, Hgb. to 100 per cent and WBC to 23,000. There were no signs of pulmonary or peripheral edema. Intermittent peritoneal lavage through a flexible sump drain was instituted: 500 cc. of the irrigating solution\* was allowed to remain for 15 minutes and then removed. 500 cc. of 10 per cent glucose in saline intravenously was given to balance the volume of aspirated gastro-intestinal fluid. The urine output for that day totalled 10 cc. Thereafter, the total fluid intake exceeded the volume withdrawn from the gastro-intestinal tract by 1,000 cc. per day.

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\*Composition and preparation of irrigating solution as in previous case.

On the following day the patient appeared less euphoric, more rational and not quite as dyspneic. By evening minimal edema of the legs was apparent. The blood NPN had fallen to 186 mg. per cent and the CO<sub>2</sub> combining power to 26 vols. per cent. The blood calcium was 5.2 mg. per cent and the blood phosphate 12.0 mg. per cent. The serum protein level was 5.27 Gm. per cent (3.16 Gm. of albumin and 2.11 Gm. of globulin). Sodium lactate (10 cc. of molar solution) and calcium gluconate (80 cc. of 10 per cent solution) were given intravenously and sodium lactate and sodium bicarbonate solution were given hourly *via* the Miller-Abbott tube. The urine output was 45 cc. Urine culture was sterile.

The next (fifth) day, temperature, pulse and respiratory rate rose sharply. The blood NPN and BUN were 170 and 147 mg. per cent respectively and the NaCl was 574 mg. per cent. The CO<sub>2</sub> combining power had dropped to 22.5 vols. per cent. Only 15 cc. of urine were obtained from the bladder. The patient expired that evening, after 8 days of anuria.

Peritoneal lavage lasted a total of 50½ hours. During that time only 37 Gm. of urea was recovered (the urea clearance varied from 1.7 to 5.6 cc. per minute). Approximate measurement indicated that of the total inflow of 52.75 liters of irrigating solution, 49.25 liters were recovered, leaving a deficit of 3.5 liters, which was retained by or absorbed from the peritoneal cavity.

Postmortem examination revealed approximately 2,000 cc. of turbid yellow fluid in the pelvis. Smear of this fluid demonstrated *E. coli*. There was a fine, flaky fibrin deposition in the pelvis and slight injection of the pelvic peritoneum extending into the lateral gutters. There was consolidation of the entire upper lobe of the right lung and patchy consolidation of the upper lobe on the left. The remaining lobes of the lungs showed moderate edema. The kidneys weighed 290 Gm. each. Microscopically they showed a lower nephron nephrosis, i.e., the glomeruli were normal, but there was necrosis, desquamation and dislocation of the tubular epithelium of the lower portion of the nephron. In addition the proximal convoluted segment showed an extreme degree of cloudy swelling and droplet degeneration. A few tubules contained reddish brown amorphous casts and were surrounded by an interstitial exudate of lymphocytes, plasma cells and eosinophiles. These findings were most marked in the corticomedullary juncture.

*Comment.* The renal damage was apparently the result of sul Diazine intoxication. No recovery of renal function was observed in the eight days the patient survived after the onset of anuria. The irrigation was inefficient for reasons that are obscure. Moreover, the infection of the peritoneal cavity was inexplicable rapid.

**Case 14.—E.A. (BIH 94529):** A 24-year-old white female was transferred in a moribund state from another hospital, where she had been treated for 40 days for progressive uremia resulting from subacute glomerulonephritis. Her daily urine output was 400-700 cc. the first week, less than 100 cc. the third week, less than 60 cc. the fourth week. The blood urea nitrogen had risen to 112 mg. per cent. The clinical course was progressively downhill, with hematemesis, occasional convulsions and eventually pulmonary edema, in spite of restricted fluid administration. It was felt that though the prognosis was grave, improvement by peritoneal irrigation might facilitate some recovery of renal function.

On admission to the Beth Israel Hospital, the patient had pulmonary edema, subcutaneous edema and ascites. The blood NPN was 308 mgm. per cent, blood urea N 236 mg. per cent, CO<sub>2</sub> combining capacity 21.5 vols. per cent, Hgb. 20 per cent, hemato-

crit 10 per cent, RBC 1.08. Intermittent irrigation\* was carried out for 21 hours. The total inflow was 17.5 liters, total outflow 17.5 liters, total urea removed 39 Gm., average blood urea clearance 8.5 cc. per minute. Thereafter the patient died. The peritoneal outflow fluid remained sterile.

Postmortem examination revealed anasarca, severe pulmonary edema and congestion, early bronchopneumonia and multiple small areas of hemorrhage in the gastric mucosa. Several fine deposits of fibrin were found in the pelvis, without evidence of inflammation or suppuration. The kidneys showed advanced subacute glomerulonephritis.

*Comment.* At this stage in our clinical experience we had concluded that to avoid absorption of irrigating fluid it should contain not less than 1% gelatin and 1% glucose. We could not determine how effective such concentrations would be for the abstraction of edema fluid. We decided to avoid gross modifications of this formula in the future except perhaps in a case such as this one, in which the edema is so threatening as to compel the emergency use of a much more hypertonic solution. This patient was near death on admission. Fluid absorption was avoided, but not enough time was available to test the ability of this formula or a similar one with greater hypertonicity to remove the retained fluid. It was clear also that in addition to the composition of the fluid, the avoidance of a stagnant pool in the cul-de-sac was essential to prevent absorption. While we were confident that we could now handle fluid and electrolyte balance effectively, the problem of the prevention and control of peritonitis still remained.

**Case 15.—E.H. (BIH 94733):** A 22-year-old man underwent partial lobectomy for bronchiectasis at another hospital. The operative procedure lasted over five hours and was followed by several hours of shock. During and immediately after operation 2000 cc. of blood were given. On the third postoperative day, because of anemia, 500 cc. of blood was given. There was no clinical evidence of transfusion reaction and no sulfonamide drug was given.

Oliguria was noted throughout the postoperative period. The total urine volume per 24 hours in the first postoperative day was 450 cc., in the second day 450 cc., in the third 280 cc. and in the fourth 136 cc. On the fourth postoperative day the blood NPN was found to be 120 mg. per cent and the patient complained of severe bilateral costovertebral angle pain.

He was transferred to this hospital. Peritoneal irrigation\* was begun the afternoon of the fifth postoperative day and was continued without interruption for 48 hours. The outflow fluid remained sterile. A substantial removal of nitrogenous material and reduction in blood NPN was accomplished (see Fig. 13 and Table VI). Urine output increased so that peritoneal irrigation was discontinued in anticipation of renal recovery. Rapid improvement in renal function occurred.

The patient was discharged in excellent condition on the twenty-first postoperative day, at which time the blood chemistry was normal, the urine was free of albumin or cells, but was alkaline and of low specific gravity. The renal urea clearance was still

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\*Composition and preparation of solution as in previous two cases except for an increase in glucose concentration to 1 per cent. Technique of irrigation as in Cases 12 and 13.

\*Composition of solution and conduct of irrigation as in the previous case.

only 40 cc/min. Two months later, the blood and urine were normal but urea clearance (47 cc/min) was still below normal.

*Comment.* The renal injury was probably due to surgical shock, although the flank pain suggests some other agent. Peritoneal irrigation was started on

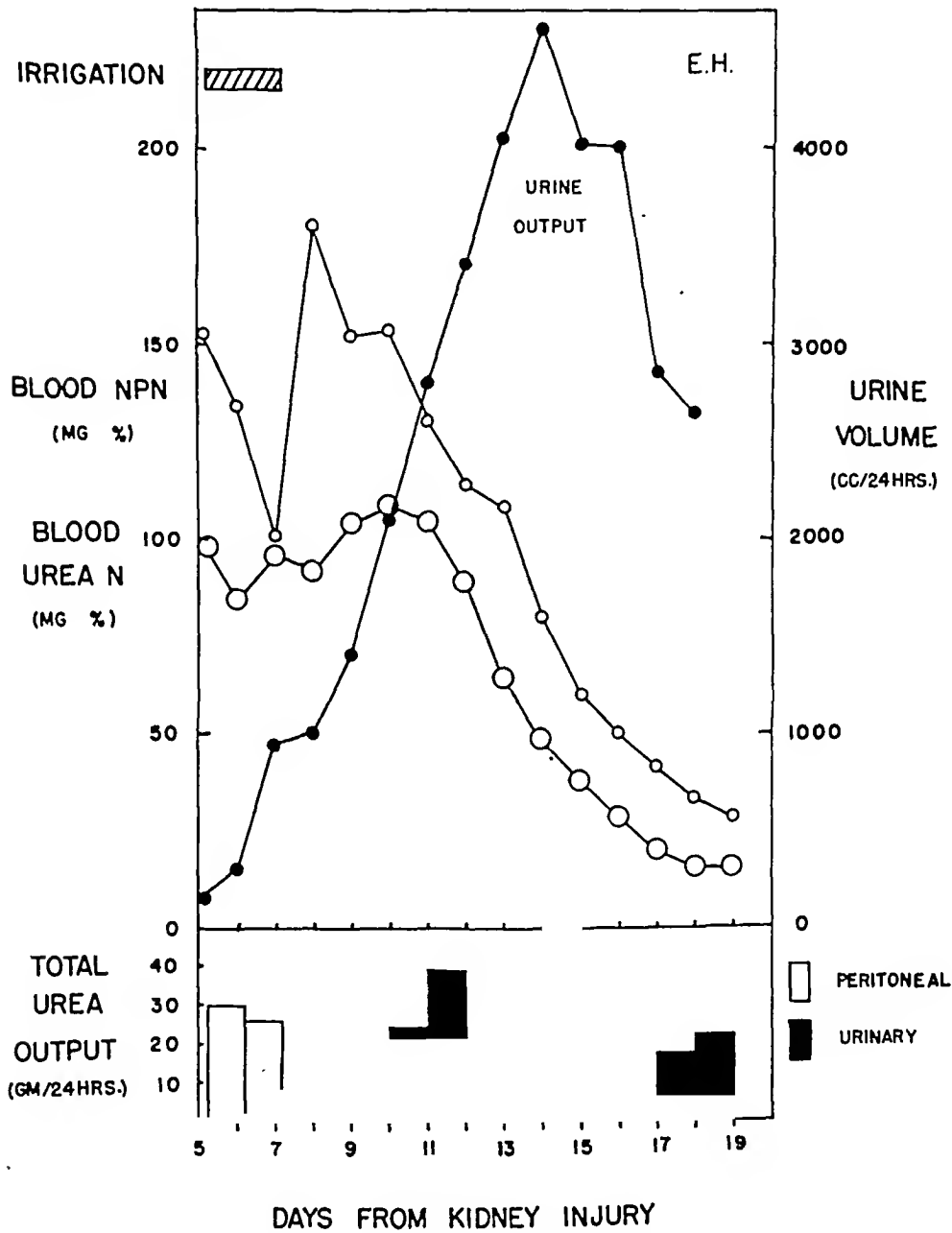


Fig. 13. Case 15.—(Cross-hatched bar indicates intermittent irrigation.)

the fifth day of oliguria and was discontinued on the seventh day, when the urine output reached 1000 cc. In spite of a linear increase in daily urine output, the blood NPN rose immediately after discontinuance of peritoneal irrigation. It was not until the 11th day, when the daily urine volume reached 3000 cc., that the urinary urea clearance value equalled the peritoneal urea clearance value. A significant decline in blood urea N then began. It is

TABLE VI—Case 15

Day (from kidney injury)	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th	19th
Peritoneal fluid:															
Urea N (mg. %)	..	44	52							..	..				
Urea clearance (cc./min.)	..	11	10							..	..				
Culture	.	sterile								..	..				
Urine:															
Urea N (mg. %)	370	332	378	415	562	507	644	624	468	658	156	292	292	390	.
Urea clearance (cc./min.)	1.84*	2.04*	4.37*	5.08*	7.7*	7.98*	11.6*	15.3	17.4	37.8	10.0	24.3	23.2*	41.0*	.
Specific gravity	1.001	1.005	1.006	1.005	1.003	..	1.002	1.008	1.004	..	..	.	1.010	1.012	1.002
Reaction	alk.	acid	acid	alk.	acid	..	alk.	alk.	alk.	..	..	.	acid	alk.	alk.
Albumin	4+	3+	3+	3+	2+	..	2+	1+	2+	..	..	.	1+	0	0
Cells	WBC	WBC	WBC	WBC	WBC	..	WBC	WBC	0	..	..	.	0	0	0
Culture	RBC	RBC	RBC	RBC	RBC	.	..	..	0	..	..	.	0	0	0
	<i>B. pyocyaneus</i>														.
Blood:															
CO <sub>2</sub> cap. (vol %)	36	32	29		57				53						
Cl <sup>-</sup> (as NaCl mg. %)	414	520	558		480		486								
PO <sub>4</sub> <sup>-</sup> (mg. %)	9.5					7.2	..	..	5.1	.		..	..	..	4.7
Ca <sup>++</sup> (mg. %)	10		10.8		10.5	10.2			10.8			..	..	..	11.3
Plasma protein (Gm. %)	5.7		5.8			5.4	6.2								
Hemoglobin (Gm. %)	12.6				11.6	..			10.8				11.3		
Arterial Blood Pressure (mm. Hg)	150 80	150 80	170 70	160 70	160 70	160 70	160 70	145 75	155 80	180 110	.	150 110			
Fluid exchange:															
Peritoneal inflow (L.)	..	28.6	23.4												
Peritoneal outflow (L.)	.	29.2	23.7					..							
Lactate M (cc.)			120	240	320	160									

\*Renal urea clearance at urine flow rates of 2 cc./min. and higher, and urea clearance by peritoneal irrigation have been calculated by the formula (15,16) for "maximal urea clearance", i.e. maximal clearance (cc./min.) =  $\frac{UV}{B}$ , where U is the concentration of urea (mg. %) in the urine or peritoneal outflow fluid, V is the flow rate (cc./min.) of urine or peritoneal irrigating fluid, and B is the average concentration (mg. %) of urea in the blood during the period of collection of urine or peritoneal fluid. The average normal "maximal clearance" value for a human adult is 75 cc./minute.

At urine flow rates below 2 cc./min. the "standard urea clearance" was calculated according to the formula (15,16): standard clearance (cc./min.) =  $\frac{U\sqrt{V}}{B}$ . The average normal "standard clearance" is 54 cc./minute.

Urinary urea clearance values marked with an asterisk are those which have been calculated as "standard clearances" and multiplied by 75/50 to facilitate comparison with the remaining "maximal clearances" in terms of the fraction of the average normal urea clearance attained.

ACUTE RENAL FAILURE

likely that recovery in this instance would have occurred without peritoneal irrigation.

**Case 16.**—J.P.M. (BIH 94966): A 22-year-old woman, received 2500 cc. of plasma and 500-1000 cc. of Type B blood for post partum hemorrhage and shock. Another transfusion of 100 cc. of Type B blood given 8 days later for anemia caused generalized pain, headache and violent vomiting. Investigation disclosed that the patient's blood type was O.

The patient voided 730 cc. of bloody urine in the first day following the transfusion reaction, and but 80 cc. of bloody urine the next day. Intravenous fluid therapy included 200 cc. of 12½ per cent glucose, 500 cc. of Hartman's solution and 1000 cc.

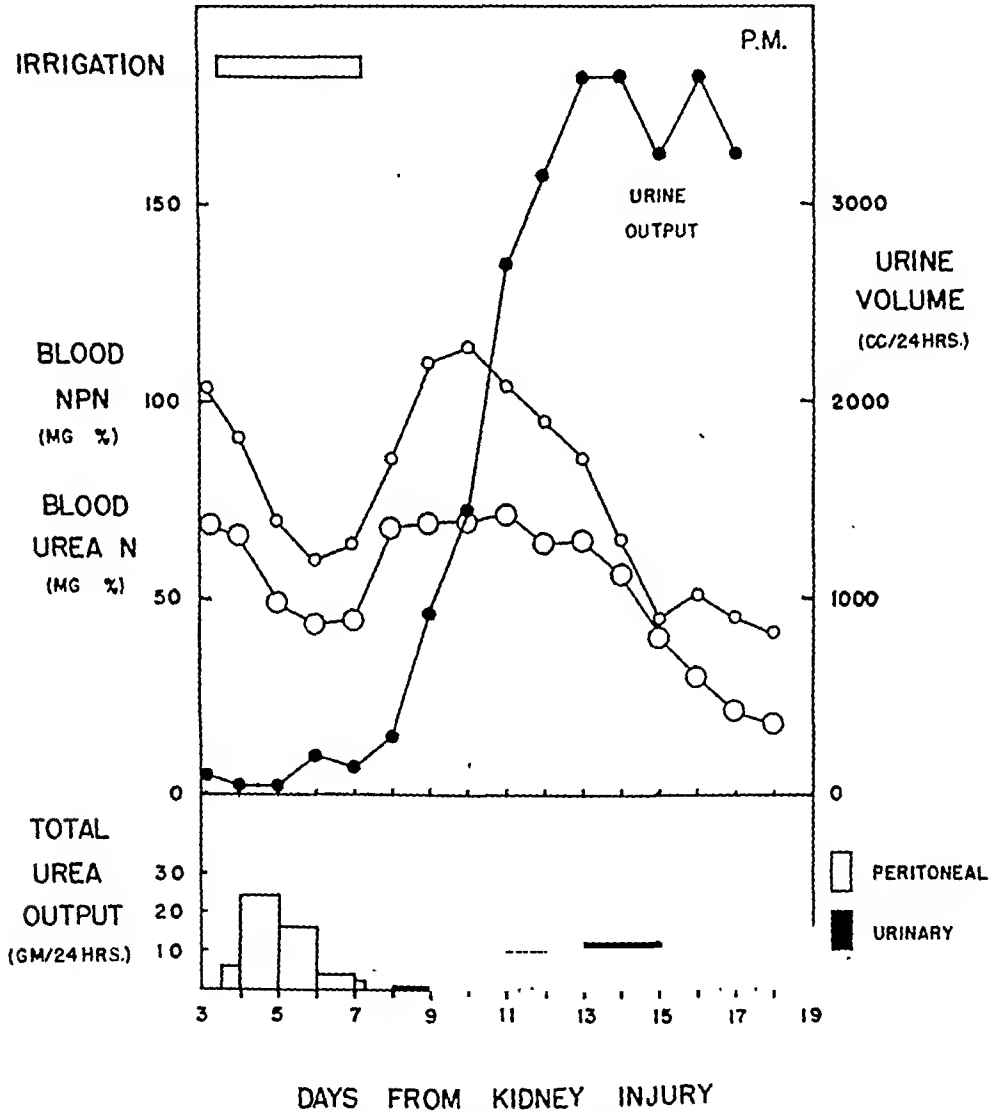


Fig. 14. Case 16.—(Open bar indicates continuous peritoneal irrigation.)

of 5 per cent glucose in water. Hot packs were applied to the costovertebral angles. On the third day following the transfusion reaction the patient voided 30 cc. of dark urine, her blood NPN was found to be 78 mg. per cent. She was then transferred to us.

Upon admission the patient was extremely pale and mildly edematous. Blood findings included RBC 2.6 million, Hgb. 50%, WBC 15,000, NPN 103 mg. per cent, CO<sub>2</sub> combining power 40 vols. per cent, NaCl 502 mg. per cent, phosphate 9.0 mg. per cent, calcium 9.7 mg. per cent. A catheterized urine specimen disclosed: sp. gr. 1003, acid reaction, albumin 4+, WBC 8-10 hpf, RBC 10-12 hpf.



TABLE VII—Case 16

Day	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th
(from kidney injury)																
Peritoneal fluid:																
Urea N (mg. %)	24	31	19	6.1												
Urea clearance (cc./min.)	11.1	13.9	9.5	3.1	<i>E. coli</i>											
Culture		sterile														
Urine:																
Urea N (mg. %)	68.6	29.3	19.5	39.5	156	205	209	201	201	146	160	161	161	215	240	
Urea clearance (cc./min.)					1.21*	1.82*	3.23*	3.76*	5.14*	5.05	6.48	8.13	10.1	20	25.5	25.7*
Specific gravity	1.003	1.011			1.008	1.008	1.004	1.007		1.008	1.002	1.003	1.004	1.004		
Reaction	acid	acid	alk.	alk.	alk.	alk.	alk.	alk.		alk.	alk.	alk.	alk.	alk.		
Albumin	4+	4+	4+	4+	4+	4+	3+	2+		2+	3+	2+	2+	2+		
Culture	<i>E. coli</i>	<i>E. coli</i>	<i>E. coli</i>	<i>E. coli</i>	<i>E. coli</i>		sterile		sterile							
Blood:																
CO <sub>2</sub> cap. (vol. %)	40	29	34	35	46		59	60								
Cl <sup>-</sup> (as NaCl mg. %)	502		604													
PO <sub>4</sub> <sup>-</sup> (mg. %)	9							6.7				7.1			3.6	
Ca <sup>++</sup> (mg. %)								6.3				8.0			9.1	
Plasma protein (Gm. %)	5.34			5.27										5.99		
Hemoglobin (Gm. %)		9.6	8.7	8.0			7.3			10.0		11.4		10.5		
Arterial Blood Pressure (mg. Hg)	110/60	110/60	120/60	120/70	130/70	120/50	110/70	110/80	140/80	110/60	104/64					130/80
Fluid balance:																
Peritoneal inflow (L.)	17.6	34.6	35.6	35.5	10.3											
Peritoneal outflow (L.)	17.8	34.8	36.0	35.5	11.0											
Lactate M (cc.)		160	320	320	160	160	80	80								
Blood (cc.)				500				500								

\*See footnote to Table 6.

*Peritoneal irrigation was carried out by a technic of continuous flow at a rate of 21-31 cc/min. from a small rubber inflow catheter in the right upper quadrant to the sump drain in the pelvic cul-de-sac. The solution was that used in the last case. Irrigation was carried out without difficulty for 89 hours. The effect upon the blood NPN and urea is shown in Figure 14 and Table 7. A total of 52.5 Gm. of urea was removed and a urea clearance value of 13.9 cc/min. was attained. The patient's clinical appearance did not change greatly.*

Auxiliary treatment during this period included: penicillin (50,000 units every three hours), water soluble vitamins given intramuscularly, 5 per cent glucose in water given intravenously (1-2 liters per day) containing 160-320 cc. of molar sodium lactate solution, two 500 cc. transfusions of type O blood, and gastrointestinal suction drainage *via* a Miller-Abbott tube.

On the last day of irrigation a few *E. coli* were found in one sample of outflow fluid. A subsequent sample gave no growth, but a smear showed scattered polymorphonuclear leucocytes containing a few phagocytosed gram negative bacilli. Streptomycin was given (0.5 Gm. intramuscularly every three hours) for one and one-half days (total 9.5 Gm.) and penicillin administration (total dosage 3.9 million units) was continued for two and one-half days thereafter. No clinical evidence of peritonitis appeared.

Two days after cessation of irrigation the blood NPN and urea N concentration rose to higher levels than those found on admission. But diuresis had started by this time so that peritoneal irrigation was not resumed. Steady improvement in renal function occurred. When the patient was discharged well twenty days after the transfusion reaction, the daily urine output was 3500 cc, with a urea content of 16 Gm. (renal urea clearance 25 cc/min), sp. gr. 1004 and 2+ albumin.

Six weeks later the patient was well. The urine was free of albumin and showed a sp. gr. of 1007. The blood urea clearance was 48 cc/mm. Blood chemistry was normal.

*Comment.* Continuous peritoneal irrigation carried out for 89 hours produced a substantial reduction in azotemia, although increasing acidosis required sodium lactate therapy. *E. coli* was grown from the peritoneal outflow fluid on one occasion on the last day of irrigation. Clinical peritonitis was not in evidence. Renal recovery first became manifest on the ninth day after the transfusion reaction and progressed so as to restore normal blood chemistry within the next six days. Significant impairment of renal function was still manifest six weeks thereafter.

It cannot be said that recovery would not have taken place without peritoneal irrigation. Spontaneous diuresis may occur in patients suffering from a transfusion reaction about the time this patient showed it, or a few days later.

**Case 17.**—A.M. (BIH 95349): A 46-year-old man with uremia, malignant hypertension, left hydronephrosis, congestive heart failure and anemia seemed moribund after eight days of hospital care. Peritoneal irrigation was requested by the attending physicians, who considered it remotely possible that the unilateral hydronephrosis was contributing to the hypertension, and that nephrectomy might be undertaken if the uremia could be corrected.

With this slim hope in mind, *continuous irrigation by an inflow catheter and sump drain at a flow rate of 25 cc/min. was started.* At that time pulmonary edema was present. The blood NPN was 186 mg. per cent, BUN 138 mg. per cent, CO<sub>2</sub>

combining power 22 vols. per cent, NaCl 332 mg. per cent, Ca 7.7 mg. per cent, phosphate 16.0 mg. per cent. Urea clearance values of 16-18 cc/min. were attained. Sodium lactate (160 cc. of molar solution), given intravenously, failed to raise the CO<sub>2</sub> combining power. A smear of the outflow fluid taken the evening of the first day of irrigation showed a few gram negative rods which did not grow in culture. *E. coli* in pure culture was grown from the peritoneal outflow fluid after 24 hours. Furacin, known to be effective against gram negative organisms when applied topically, was added to the irrigating solution to a concentration of 1/40,000.\* The peritoneal outflow fluid yielded no growth one hour after the Furacin was added to the irrigating solution, but a culture taken five hours later showed a small growth of *E. coli*.

The patient's general condition remained very poor and he expired after 36 hours of peritoneal irrigation.

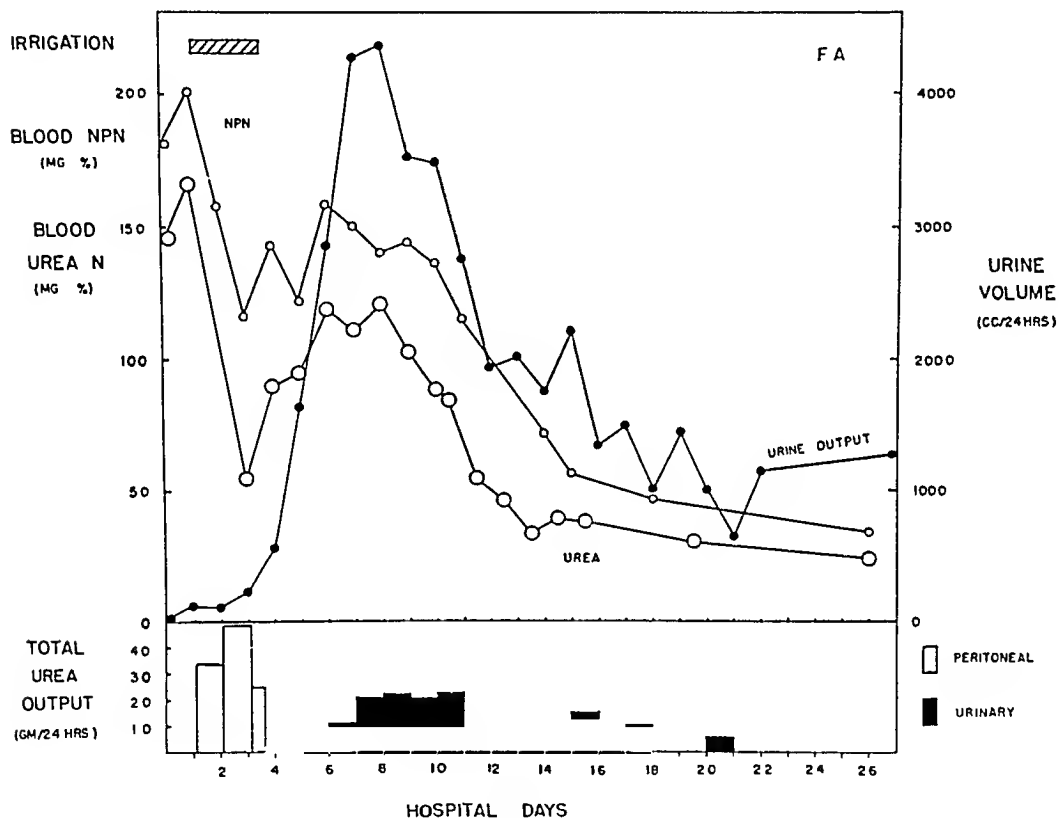


Fig. 15. Case 18.—(Cross-hatched bar indicates intermittent peritoneal irrigation.)

The amount of protein removed\*\* by the irrigation was 71.7 Gm. in 36 hours.

Postmortem examination disclosed no evidence of peritonitis. There was enlargement of the heart and pulmonary edema and congestion. There was a stricture at the left uretero-vesical junction with marked dilatation of the left ureter and kidney pelvis, both of which contained purulent fluid. The histologic examination of the kidneys disclosed necrotizing arteriolitis, arteriosclerosis and arterio-sclerosis.

\*Furacin in this concentration was found to be effective against *E. coli* *in vitro* and to a lesser extension *in vivo* (17). Experiments on dogs suggested that the toxic effects of absorption of Furacin would be avoided at this concentration.

\*\*The method of analysis for the protein was as follows: 50 cc. samples were brought to a pH of 4.8-4.9 by the addition of 100 cc. of an acetate buffer solution, boiled for thirty minutes and then filtered. The precipitates were washed, dried and weighed. No protein is recovered as a precipitate from the irrigating fluid itself.

# ACUTE RENAL FAILURE

TABLE VIII—Case 18

Hospital day	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	14th	17th	20th
Peritoneal fluid:													
Urea N (mg. %)	87	60-67	59-52	..	..	..	..	..	..	..	..	..	..
Urea clearance (cc./min.)	10	14-20	19-13	..	..	..	..	..	..	..	..	..	..
Culture	<i>B. subtilis</i>												
Urine:													
Urea N (mg. %)	133	149	158	168	188	187	231	255	274	299	326	294	287
Urea clearance (cc./min.)	..	..	12*	1.5*	2.6*	3.1*	5.9	6.3	6.0	7.5	12.5*	10.9*	10.9*
Specific gravity	..	..	1.008	1.005	1.010	1.010	..	1.010	1.008	1.018	1.005	1.007	1.013
Reaction	..	..	alk.	alk.	alk.	alk.	..	alk.	alk.	alk.	alk.	alk.	acid
Albumin	..	..	4+	3+	2+	2+	..	1+	1+	2+	1+	0	0
Culture	<i>E. coli</i>	..	..	..	..	..	..	..	..	<i>aerogenes</i>	1+	0	0
Blood:													
CO <sub>2</sub> cap. (vol. %)	28	28	25	35	35	33	38	39	..	..	..	..	..
Cl <sup>-</sup> (as NaCl) (mg. %)	480	..	606	592	440	..	..	548	..	..	..	..	..
PO <sub>4</sub> <sup>-</sup> (mg. %)	11.1	..	10.5	..	8.3	..	3.6	..	..	7.0	..	..	..
Ca <sup>++</sup> (mg. %)	4.8	..	6.9	..	10.5	..	8.9	..	..	8.2	..	..	..
Plasma protein (Gm. %)	6.7	..	12.5	10.1	..	5.6	10.1	..	..	10.4	..	10.1	10.1
Hemoglobin (Gm. %)	..	..	..	..	..	8.7	..	..	..	..	..	..	..
Arterial Blood Pressure (mg. Hg)	175/85	200/100	195/90	190/100	175/90	170/90	170/100	155/80	..	155/95	120/70	130/70	..
Fluid exchange:													
Peritoneal inflow (L.)	15.3	35.6	24.5	..	..	..	..	..	..	..	..	..	..
Peritoneal outflow (L.)	15.0	33.9	24.3	..	..	..	..	..	..	..	..	..	..
Lactate M (cc.)	160	240	160	..	..	..	..	..	..	..	..	..	..
Blood (cc.)	500	500	..	..	..	..	..	..	..	..	..	..	..

\*See footnote to Table 6.

*Comment.* This patient was moribund when irrigation was started. Nitrogen removal proceeded efficiently, but survival was not long enough to effect a significant change in the uremic state. *E. coli* appeared in the peritoneal outflow fluid within 12-24 hours.

Case 18.—F.A. (BIH 97808): A 39-year-old female was transferred to the Beth Israel Hospital because of post-eclamptic oliguria and uremia six days after Caesarean section. Pre-eclampsia during pregnancy three years earlier had been terminated by Caesarean section because of a deformed pelvis. On admission there was pitting edema, the arterial pressure was 150/90 mm. Hg., the fundi were normal, the blood NPN was 186 mg. per cent and the CO<sub>2</sub> combining power 20 vols. per cent.

The patient was observed for about 20 hours, during which her condition deteriorated considerably. She became drowsy and apathetic and exhibited hypocalcemic twitchings and tetany. The bladder contained 25 cc. of turbid, alkaline urine with a sp. gr. of 1003, albumin (4+), red and white cells, *E. coli*, gram-positive cocci and diphtheroids. At this time the blood NPN was 202 mg. per cent, the serum calcium 4.8 and the serum phosphate 11.1 mg.

The intestine was intubated. *Intermittent peritoneal irrigation was carried out with 500 cc. volumes of solution (1% gelatin and 1% glucose) which were removed after a ten-minute period.* The patient seemed moribund during the first 12 hours, but thereafter clinical improvement concomitant with improvement in blood chemistry occurred (Table 8 and Figure 15). The intravenous fluid was limited to 1000-1500 cc. per day, which included whole blood, 15 per cent glucose in water, molar sodium lactate solution (160-240 cc.) and 10 per cent calcium gluconate (30 cc. or more). Penicillin and the water soluble vitamins were given intramuscularly. Irrigation was terminated after 60 hours. The sump was removed. *B. subtilis* was found in the outflow fluid throughout the irrigation period. There were equivocal signs of peritoneal infection, which disappeared when the irrigation was stopped.

Diuresis began within a day after the cessation of irrigation (10 days after renal shutdown). In spite of rapidly increasing urine volumes the recovery of concentrating power was slow, so that a secondary rise in blood nitrogenous levels occurred. During the next four weeks she regained mental clarity, a normal arterial pressure and clinical well-being. Nausea and vomiting were the last symptoms to disappear. On discharge the blood chemistry was normal, the urine was acid, free of albumin or sediment with a sp. gr. as high as 1.018. Renal blood urea clearance, however, was less than 1/7 of normal.

*Comment.* Little is known of this patient's renal function prior to the eclamptic convulsions. The slow renal recovery after the onset of diuresis and the markedly reduced function at the time of discharge suggest reduced renal function prior to the second pregnancy. The patient was so sick when irrigation was started that it is doubtful if she would have survived long enough to permit spontaneous renal recovery. For this reason we believe that the irrigation therapy was responsible for the induction of diuresis. *B. subtilis* is considered non-pathogenic. It was the sole organism recovered from the peritoneal outflow fluid. Its pathogenicity in this case was not determined.

#### DISCUSSION

Of the group of 18 patients, in this and a previous report, 4 recovered and 14 died (Table IX). Of the 14 patients who died, 5 had renal lesions which can be assumed to have been irreversible, 8 had lower nephron injuries and

1 had tubular nephritis. Death could be attributed to uremia or pulmonary and cerebral edema in 5 of these cases, to peritonitis which resulted from irrigation in 3, to postpancreatectomy peritonitis in 1, in lesser degree to peritonitis in 3, to pulmonary embolus in 1 who had recovered renal function, and to terminal carcinoma in 1.

The cause of renal failure in the 4 who survived was sulfathiazole sensitivity, surgical shock, incompatible blood, and eclampsia. In the case of surgical shock, the return of renal function would almost certainly have ensued without peritoneal irrigation.

TABLE X\*—*The Occurrence of Peritoneal Infection During Irrigation*

Case	Organisms	Appearance of positive cultures (day of irrigation)	Total duration of irrigation (days)
1	0	..	two 2 day periods
2	<i>E. coli</i>	12	12 (discontinuous)
3	<i>E. coli</i>	3	7
4	<i>E. coli</i> , <i>staph. albus</i> , <i>Cl. welchii</i> , <i>enterococci</i>	6	6
5	0	..	2
6	<i>E. coli</i> , gram positive diplococci, <i>B. pyocyaneus</i> , <i>B. subtilis</i>	7 10	10
7	(streptococci and diphtheroids) <i>E. coli</i>	(before irrigation) 3	7½
8	<i>E. coli</i> , <i>B. aerogenes</i> , Friedlander's bacillus	7	7
9	0	..	1½
10	<i>Staph. albus</i> and diphtheroids <i>E. coli</i> <i>E. coli</i>	2½ 2 days later 4 days later	2½
11	<i>E. coli</i>	4½	6
12†	0	..	2 (44 hours)
13†	<i>E. coli</i>	2	2 (50 hours)
14†	0	..	1 (21 hours)
15†	0	..	2 (45 hours)
16	<i>E. coli</i>	4	4
17	<i>E. coli</i>	1	1½
18†	<i>B. subtilis</i>	1	2½

\*We are indebted to Dr. Fritz Schweinburg of the Department of Surgical Research for bacteriologic studies.

†Irrigation by intermittent (filling and emptying) technic.

(Note: Flexible sump drain used in case 12 and thereafter. Irrigation by continuous technic except as noted above).

These mortality data, however, are of no great significance. These patients, who could be expected to die, were, we believe, justifiably utilized as experimental subjects for the purpose of perfecting a hopeful therapeutic technic which was and still is in an evolutionary stage.

*Peritonitis* (Table X): It is obvious that this method is not a clinically acceptable one unless and until it can be utilized with reasonable assurance that peritonitis will not occur or will be curable if it does occur. In only 6 of the 18 patients reported in this and in the previous paper, did the peritoneal outflow fluid remain sterile throughout the period of irrigation and none of these six patients was irrigated for longer than 48 hours at a time. In two of the other 12 patients organisms were found in the outflow fluid

after 24 hours, in four after 72 hours, in five between 4-7 days and in one (Case 2) after twelve days of discontinuous irrigation. *E. coli* was found in 11 of the 12 patients, in eight in pure culture and in the remainder with *B. pyocyaneus*, gram-positive diplococci or *B. aerogenes*. In one case mixed organisms, including anaerobes, were recovered just before death, but the peritoneum was entirely free of reaction. In one patient with a prior post-operative streptococcal peritonitis, *E. coli* was grown in pure culture after three days of irrigation.

In half of the 12 patients with positive cultures from the outflow fluid, clinical and postmortem evidence of peritonitis was either lacking or equivocal. In the other half the intensification of antibiotic therapy when the positive cultures were obtained did not ameliorate the course of the peritonitis. But cessation of irrigation was followed by recovery from peritonitis and survival in two of these.

Since the sterility of the inflow fluid was not in doubt at any time, the other likely source of bacterial contamination was the sinus tract leading from the skin to the peritoneal sac. But organisms native to the skin and not susceptible to penicillin therapy (e.g., staph. albus, sarcinae, diphtheroids) were only rarely found in the peritoneal fluid. Since the special care given in the preliminary treatment of the skin, the protection of the abdominal wound and in the design and application of the sump drain and effective filtration of the air failed to prevent peritoneal infection with *E. coli*, it is conceivable that serosal irritation produced by peritoneal irrigation may have facilitated transmural migration of this organism from the intestinal canal.

In normal and nephrectomized rabbits and dogs following the intraperitoneal injection of a strong irritant *E. coli* was recovered in pure culture from the peritoneal cavity<sup>18</sup>. In a dog with *E. coli* peritonitis induced by an irritant, *E. coli* tagged with radioactive iodine was introduced into the gastrointestinal tract. Twenty-four hours later radioactivity to the extent of 0.1 per cent of that given was found in the washed peritoneal fluid sediment<sup>19</sup>. The irrigating solution used in patients failed to produce positive cultures in the peritoneum of normal dogs after ten days of filling and emptying the peritoneal cavity twice each day<sup>18</sup>. Dogs similarly treated after having been rendered uremic by bilateral nephrectomy, showed *E. coli* within six to nine days, except for those animals in which the *E. coli* of the intestinal canal had been eliminated by starvation plus intensive enteric administration of streptomycin and sulfaphthalidine<sup>18</sup>.

The more rapid appearance of *E. coli* in uremic patients than in uremic animals may be due to the far greater resistance of dogs to this organism and to the more continuous exposure to the irritant in patients than was the case in the animal experiments.

Thus, it appears that migration *E. coli* through the bowel wall occurs more readily in the uremic state. This, both in man and animals, may be due

TABLE XI—Urea Clearance by Peritoneal Irrigation:  
Flow rate and urea clearance during 24 hours of best performance in each patient. Comparison of continuous flow with filling and emptying technic.

Case Number	CONTINUOUS			Case Number	INTERMITTENT		
	Flow Rate (cc./min.)	Urea Clearance (cc./min.)	Averages Flow Rate		Flow Rate* (cc./min.)	Urea Clearance (cc./min.)	Volume Introduced at Each Filling (cc)
2*	13	8	16	11	10-15	11	1000
2*	16	14		15	14	11	500
4	17	12.5		13	15	6	500
11	20	10		14	18	9	500
9	23	3		12	21	12	500
16	25	14		Average	16	10	
5	25	22					
10	26	19					
17	29	18.5		18	22.4	19.9	500
3*	29	21					
8	30	16	39	*Calculated from total volume introduced into the peritoneal sac each 12 or 24 hours. †Equilibration period in each cycle, i.e., time from end of introduction of fluid to start of withdrawal.			
7	33	22					
3	35	19					
6	37	34					
2	40	28.5					
1*	45	16					
1	60	23					
General average	31	18.5					

\*Less than optimal flow rates included for comparison; not included in general average.



to a change in the physical state of the intestinal wall as well as to lowered resistance to contaminating organisms.

Since the evidence points to the intestine as the source of offending bacteria, an effective bactericidal agent for *E. coli* must be found. Streptomycin has been found to be of little or no therapeutic value, although its oral use for the preliminary reduction of intestinal bacteria has not been tested. The effectiveness of the newer antibiotics, i.e., polymyxin, bacilloporon B or duomycin will be examined in future cases.

Since the likelihood of infection increases with the duration of the irrigation period, the latter for the time being should be limited to 2-3 days. If contamination has already occurred, a rest period will in some instances allow the peritoneum to sterilize itself. Since such a rest period may be required, it is obviously desirable to utilize the method so as to obtain maximum dialyzing speed.

*Efficiency of Peritoneal Irrigation:* While the severity of the uremic state is not due to the azotemia, it varies roughly in parallel with the blood

*Fluid Absorbed from Peritoneum During Irrigation:*  
TABLE XII—Peritoneal fluid retained (density of outflow compared to inflow) during the 24 hours of irrigation which provided the best urea clearance.

CONTINUOUS*				INTERMITTENT*				
Case	Non-electrolyte content of irrigating solution		Fluid retained (cc.)	Case	Cycle (min.)	Non-electrolyte content of irrigating solution		Fluid retained (cc.)
	Glucose(%)	Gelatin(%)				Glucose(%)	Gelatin(%)	
7	2	..	1000	12	15	0.5	1	700
8	2	..	4000	13	15	0.5	1	2000
11	1	0.5	4000	11	45	1	0.5	700
10	0.5	1	5900	14	15	1	1	0
17	1	1	100	15	15	1	1	—600
16	1	1	—200	18	10	1	1	600

\*Flexible sump drain used in Case 12 and thereafter.

nitrogen level. To reduce the blood NPN by one-half in 48 hours, the blood urea clearance by peritoneal irrigation must be at least 20 cc/min. A clearance rate of 7-10 cc/min. may prevent a further rise in the blood NPN level or accomplish a very slow reduction, over a period of days. A few of our patients showed such a poor urea clearance, for which we cannot account.

It is not yet decided whether continuous or intermittent irrigation provides the more efficient dialysis. Table XI suggests that a flow rate of at least 25 cc/min. is required to produce maximal clearance by continuous irrigation. To obtain a corresponding value by the intermittent technic requires the use of shorter cycles than were used except in the last case. Analysis of Table XI indicates that, within the conditions tested, the efficiency of urea clearance is determined by the overall flow rate and not by the type of irrigation. High flow rates are readily accomplished by continuous irrigation without inconvenience to patient or attendants. A further

increase in overall flow rate by intermittent filling and emptying might be accomplished by further shortening the equilibration period or by an increase in the volume of fluid introduced at each filling. In many patients the latter is limited by the discomfort of abdominal distentions or by interference with breathing. Intermittent irrigation has the disadvantage of requiring the continuous attention of a trained attendant.

Table XII shows that the least fluid absorption occurred when 1% glucose and 1% gelatin were used to produce hypertonicity. In this respect continuous and intermittent irrigation were equally satisfactory with this solution. The composition of the fluid alone may not be wholly responsible for the avoidance of fluid absorption, since the flexible sump drain, which prevents puddling in the pelvis, was used with this fluid in all instances.

*Edema.* When oliguric patients are seriously overhydrated, not only is the intravenous therapy needed for the control of acidosis and starvation impeded but the problem of removal of excess fluid is created. Pulmonary and cerebral edema commonly cause the death of oliguric patients. A good deal of fluid may be removed by suction drainage of the intestine. If the edema is so severe that it is desirable to decrease it rapidly, increasing the hypertonicity of the dialyzing solution may be attempted. This must be done with caution. In Case 4 a solution of 5% gelatin and 2½% glucose withdrew fluid from the plasma so rapidly as to produce shock. Moreover, the hypertonicity may be responsible for the peritoneal irritation and by increasing it still further, infection may be even more likely. Excessive sodium administration and unreplaced protein loss contribute to generalized edema in the oliguric phase and delay diuresis. Anuria in tubular lesions may be due to obstruction to tubular flow from the inflammatory renal edema together with reabsorption of the entire glomerular filtrate rather than to decline in glomerular output<sup>20</sup>. If the kidney is rendered still more edematous by overhydration, diuresis is still further interfered with<sup>21</sup>. The omission of sodium chloride from the irrigating fluid rapidly abstracts it together with water from the extracellular fluid but such a rapid removal of body sodium so reduces the "available alkali"<sup>22</sup>, the plasma volume<sup>23</sup>, and the interstitial fluid volume as to be dangerous, apart from the simultaneous occurrence of intracellular overhydration<sup>24</sup>. Indeed, such salt loss may have been responsible for the failure of early clinical efforts in which peritoneal irrigation was carried out with simple glucose solutions (see reference 2).

*Acidosis.* Peritoneal irrigation with the solutions ordinarily used does not correct the progressive acidosis of uremia. While the total base in the solution is that of normal plasma, the chloride content is considerably higher and the bicarbonate considerably lower (see Fig. 9). Little of the total base, therefore, is available to neutralize the excess of acid radicles. Modification of the formula by the replacement of excess chloride by bicarbonate or lactate corrected the acidosis of two of three patients in whom it was tried, but the resulting alkalinity of the irrigating fluid may have contributed to

peritoneal irritation and infection. It is, therefore, considered inadvisable to use the more alkaline solutions routinely. The acidosis is better-treated by providing as much carbohydrates as can be given so as to impede ketosis and reduce protein catabolism and by giving alkali intravenously. Uncorrected acidosis may impede the recovery of renal function<sup>20</sup>.

*Nutrition.* The biochemical disorder in the uremic patient may be aggravated by the loss of protein into the irrigating fluid. The outflow fluid contains a heat coagulable protein, which has been measured in recent cases and found in concentrations varying from 20-220 mg. per cent. Still larger protein loss during peritoneal irrigation has been reported by others<sup>7, 11, 25</sup>. The total amount of protein lost in this way in our cases has been as much as 72 Gm. in 36 hours. Larger losses may occur when peritonitis sets in.

Since oral feeding is, as a rule, precluded because of ileus and since intravenous amino-acid feeding is severely limited because of the limited water allowance, whole blood and plasma are given for hemoglobin or plasma protein deficiency. The basal caloric requirement (1600 calories) cannot be met by intravenous feeding. Glucose in excess of 15% is undesirable because of its hypertonicity and the possibility of renal tubular damage<sup>26, 27, 28, 29</sup>, although this may not be a serious factor if the infusion is given very slowly. One liter of 15% glucose provides only 600 calories. Absorption of glucose from the irrigating fluid varies with the concentration. The total absorption of glucose from a solution with a one per cent concentration has been found during continuous or intermittent irrigation to be only 4-5 Gm. per hour, or 96-120 Gm. per day, i.e., 360-480 additional calories. Hence starvation ketosis with acidosis is not completely prevented and usually requires alkali therapy.

*Potassium and Magnesium.* Although potassium is excreted in marked renal insufficiency so long as urine is secreted<sup>30</sup>, so that potassium accumulation is rarely significant in chronic uremia<sup>31, 32</sup>, potassium intoxication might become an important or even lethal factor in anuria<sup>33</sup>. Toxic levels of serum potassium in acute uremia have been reported<sup>34, 35, 36, 37</sup>.

The excess potassium in uremia is probably eliminated by peritoneal irrigation. The irrigating solution contains potassium in a concentration equal to that in normal plasma (5 mEq/L) to prevent potassium depletion. Should Potassium intoxication occur potassium should be omitted from the solution and intravenous sodium and calcium therapy applied<sup>37, 38</sup>. Experimental<sup>39, 40</sup> and clinical<sup>41</sup> studies indicate that the administration of potassium (whether in the form of food, diuretic salts, or fragile transfused red cells) to severely oliguric patients should be avoided.

Similar considerations may apply to magnesium, but no increase in plasma magnesium was found in 13 recently reported instances of acute uremia<sup>35</sup>. Calcium is stated to be a specific antagonist of magnesium poisoning<sup>42</sup>.

*Calcium and Phosphate.* An increase in serum phosphate and reduction in serum calcium, regularly reported in chronic<sup>32</sup> and acute<sup>35</sup> uremia, are

among the most striking of the chemical alterations observed in our patients. Calcium concentrations as low as 4.8 mg. per cent and phosphate as high as 11.1 mg. per cent are found. Tetany and convulsions are common, but these respond to intravenously administered calcium chloride or calcium gluconate. In certain acidotic patients, alkali therapy precipitates tetany, as would be expected because of the already low ionic calcium. Hyperphosphatemia is among the last of the chemical abnormalities to be corrected by peritoneal irrigation. In surviving patients a return to normal does not occur until some days after diuresis has set in. For these reasons, the phosphate salt has been omitted and the  $\text{CaCl}_2$  concentration doubled in the irrigating solution. Even so there is need for intravenous calcium therapy. No systematic effort has been made to eliminate hypocalcemia by calcium feeding.

*Adjuvant Therapy.* Penicillin is given in large doses prophylactically. Streptomycin is given only if infection of the peritoneum or the urinary tract due to a susceptible organism occurs. It is not given prophylactically because of the rapid development of bacterial resistance. Sulfonamides are not given parenterally as a routine measure for fear that they might further damage the kidney, although this fear may not be warranted.

The water soluble vitamins are given parenterally in large doses in view of the likelihood that they are dialyzed out of the plasma by peritoneal irrigation, although there is no experimental evidence that this does happen. Only fresh blood is used for transfusion in order to avoid renal damage from a rapid breakdown of any considerable fraction of the infused cells.

An effort is made in all patients to pass the tip of a Miller-Abbott tube beyond the pylorus before starting peritoneal irrigation.

*Renal Recovery.* The pattern of renal recovery in our patients (and in those reported by others<sup>43</sup>) appears to consist first in a return of glomerular function followed by a slow improvement in tubular function. Following the onset of diuresis, there is usually a nearly geometric progression in the daily urine volume\* to a maximum of 4 or 5 liters (3 cc/min), after which the volume declines. A urine volume as high as 9 liters per day (6 cc/min.) in this phase has been reported<sup>45</sup>. The urine has a specific gravity of 1.003 to 1.010, tends to be alkaline and has a urea concentration no greater than twice that of the plasma. Further evidence of inadequate renal function in this phase is the large loss of sodium chloride<sup>45</sup> which may produce rapid dehydration, if not anticipated and replaced. Thereafter, the urinary urea increases in concentration, and the blood urea clearance rises above 7.5 to 10 cc/min., with a concomitant fall in blood NPN. As the specific gravity rises signifying improved tubular function, the urine becomes acid, and the acidosis and hyperphosphatemia disappear. Complete tubular recovery was not observed in our surviving patients even after some months.

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\*These volumes remain well below the average normal glomerular filtration rate—120 cc/min and even well below the maximum urine flow of normal man—20 cc/min (44).

*Selection of the Patient and Initiation of Irrigation:* Patients in acute renal failure should not be considered suitable for dialysis therapy unless clinical evaluation indicates that the injury responsible for failure is reversible. This is often difficult to determine. Bichloride of mercury, carbon tetrachloride or other drug poisoning, toxic injury from acute infections, incompatible blood transfusion, traumatic shock, crush syndrome, acute nephritis, anuria complicating eclampsia, or acute renal damage superimposed on chronic renal disease which has been compatible with life, are examples of disorders that may be acceptable for dialysis. In many patients the renal failure is only one among several grave disorders, any of which may prove lethal even if renal recovery is possible.

Peritoneal irrigation does not heal the renal lesion. It simply reduces azotemia and improves electrolyte and fluid balance for a length of time which, it is hoped, will be sufficient to permit recovery of renal function.

Since the treatment to be applied should carry the smallest possible risk, there is much to be said for conservative treatment without resort to any special procedure. Many patients with acute renal lesions, if carefully managed, can recover even after two weeks of uremia<sup>45</sup>. Although occasional anuric patients have been observed to survive for as long as 3-4 weeks<sup>46, 47</sup>, death usually supervenes within 10-14 days if recovery of renal function does not occur. There is widespread misunderstanding as to what the circumstances require. As a result patients in uremia are made worse and sometimes succumb to the burdens inflicted by unwise therapy. Overhydration is a common therapeutic abuse resulting in death from pulmonary or cerebral edema. On the other hand, dehydration will delay diuresis. Appropriate fluid and electrolyte therapy requires frequent reappraisal of the state of imbalance. What is lost by vomiting or diarrhea, by visible sweating and in the urine must be replaced. Not over 1000 cc. over and above this total is to be given daily, whether parenterally or orally. To this 1000 cc., 100-150 grams of dextrose and water soluble vitamins are added. Alkali and calcium are also added, as needed. Sodium chloride is not given except as it is lost in substantial amounts from the stomach. The small amount lost *via* the skin is not significant. Moderate hypochloremia *per se* produces no symptoms and requires no therapy, while excess salt may prove disastrous. An effort is made to maintain optimal conditions for urine production in terms of cardiac output, blood volume, arterial pressure, and hemoglobin concentration.

If oral alimentation is possible, it must respect the foregoing fluid and electrolyte requirements. A non-distending carbohydrate is desirable since the requirement for dextrose cannot be met by intravenous therapy. Protein may be given also, even though nitrogenous residues cannot be excreted, for it is extremely doubtful that the azotemia itself is seriously deleterious in uremia. By a regimen of this sort, survival can be anticipated in many types

of acute renal failure which are capable of reversing themselves within two to three weeks.

Other technics are also available. Trueta's studies<sup>48</sup> suggest that neurogenic diversion of renal cortical blood flow may account for some types of acute renal failure. Abolition of this reflex by prolonged or fractional spinal anesthesia, splanchnic block or renal denervation deserves more study.

At the present time, however, dialysis of the blood is the only direct approach with some promise of therapeutic benefit, but peritoneal dialysis cannot expect to become an acceptable method until an effective antibiotic against contaminating organisms is found. One can scarcely anticipate as rapid and complete a removal of retention products by peritoneal dialysis as by Kolff's dialyzer<sup>49</sup>. The clinical problem varies so widely from one case of renal failure to another that flexibility of adaptation is essential no matter which of the two methods is used. If the Kolff technic can be controlled in all 29 aspects and made sufficiently flexible to meet the requirements of each case it has obvious advantages and a wider margin of safety than peritoneal dialysis. Experience will eventually decide the possibilities and advantages of each method. The introduction of a long aspirating tube into the ileum combined with an irrigating fluid which contains sodium sulfate to withdraw retention products into the gut has recently been reported to give good urea clearances<sup>50</sup>.

When in the course of the uremic state any one of these measures should be applied remains an open question. Advocates of conservative therapy would presumably welcome them only when a progressively rapid deterioration is in evidence. This may be too late for any therapy. If, as is so often the case, the patient comes under observation in an already far advanced state of renal failure, it will be difficult to defend the exclusive use of conservative measures if rapid dialyzing technics are at hand. The fact that diuresis frequently sets in soon after blood levels of NPN and urea nitrogen show a substantial fall suggests that the uremia itself may act as a block to recovery of renal cellular function. For this reason it may be desirable to institute such treatment early rather than late.

If further study affirms the validity of this concept, the prospect of accelerating return of renal function will be better than is now possible by good conservative therapy alone.

#### CONCLUSION

Data obtained in 14 additional patients in renal failure are presented and evaluated. The present method of performing peritoneal irrigation is described, and various aspects of the care of the patient in renal failure are discussed. The continuing hazard of peritonitis makes it necessary to regard the method as still in the experimental stages, and should not be considered for routine clinical use.

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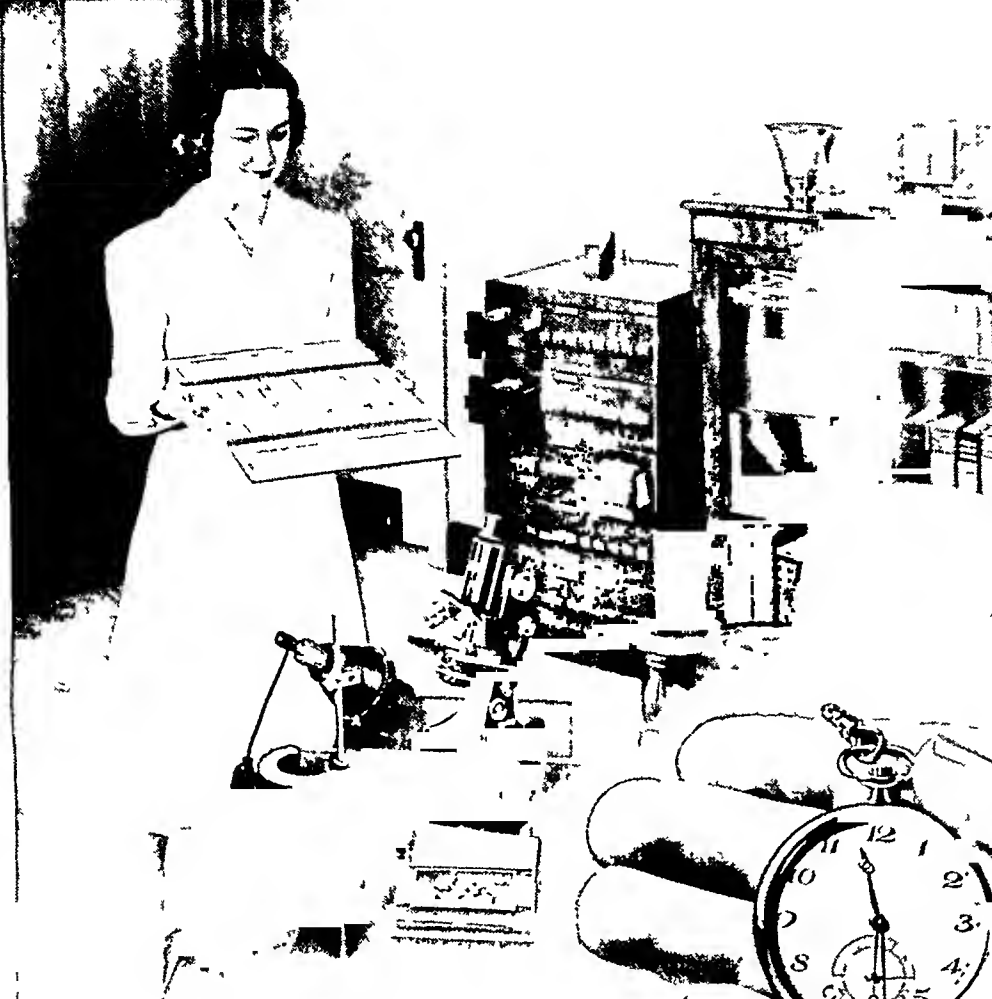
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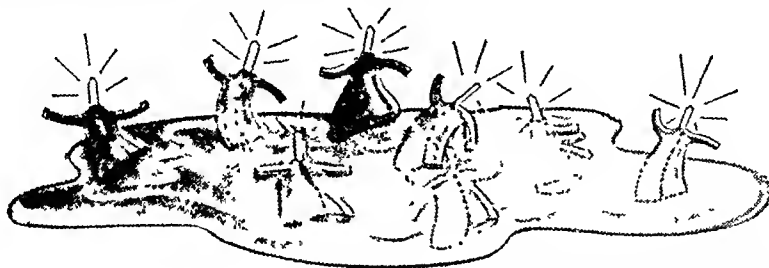
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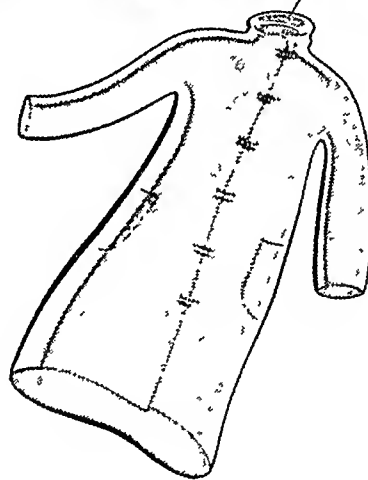


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## RECURRENT ACUTE PANCREATITIS: OBSERVATIONS ON ETIOLOGY AND SURGICAL TREATMENT \*†

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THE WIDE USE OF SIMPLE LABORATORY PROCEDURES for the determination of serum amylase has revealed several facts regarding pancreatitis.

1. It is a common disease and varies in intensity from mild attacks to a fulminating catastrophe. Fortunately the latter event is a small proportion of the total cases.

2. Recurrence is common and may be anticipated. With repeated attacks there may be progressive destruction of functioning pancreatic tissue with pathologic changes in the gland and deficiencies in external and internal secretions.<sup>1</sup> On the other hand, in some patients after many years of recurrent attacks no measurable or visible changes occur in the gland.

3. Pancreatitis is frequently associated with biliary tract disease. Many disorders heretofore termed post-cholecystectomy syndrome, biliary dyskinesia etc. are actually recurrent attacks of pancreatitis.<sup>2</sup>

Previous factual knowledge has been available for many years, since Opie<sup>3</sup> in 901 described the reflux mechanism. This is dependent on an anatomic variation in the entrance of the main pancreatic duct to the duodenum which creates a common biliary-pancreatic passageway, thus permitting bile to flow into the pancreas. The immediate bile diverting mechanism in Opie's case was a stone lodged in the ampulla of Vater. Archibald,<sup>4</sup> in 1919, showed that a similar bile diverting mechanism could be brought about by spasm of the sphincter of Oddi.

The effectiveness of surgical management of the disease has not kept pace with the knowledge of what must be the mode of production in at least

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\* Aided by a grant from the National Institute of Health, United States Public Health Service, Grant # RG 807.

† Read before the American Surgical Association, Quebec, Canada, May 27, 1948.



a large number of cases. Decompression of the biliary tract by drainage to prevent reflux is effective only so long as the drain remains. Sympathectomy to interrupt pain sensation is not a direct attack on the disease. Section of the esophageal vagus to paralyze the sphincter of Oddi might be effective but it deprives the gastro-intestinal tract of that innervation. Local nerve interruption<sup>5</sup> seems rational but is technically difficult and its effect is temporary,

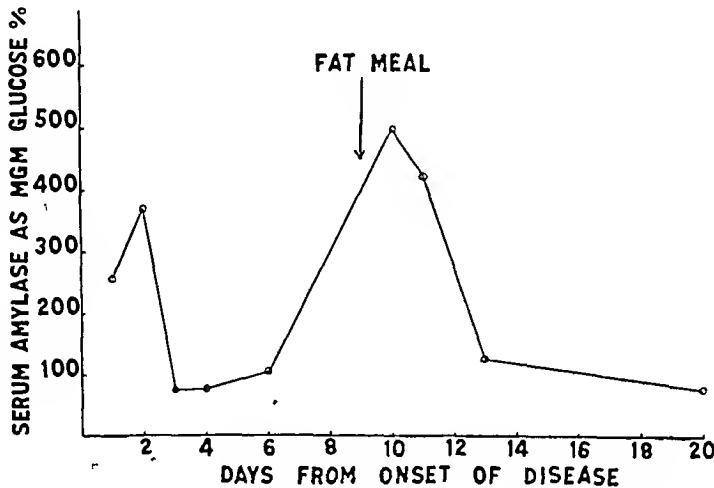


FIG. 1.—(Case 13) Serum amylase determinations demonstrate recovery from an attack of acute pancreatitis and recurrence following administration of a fat meal.

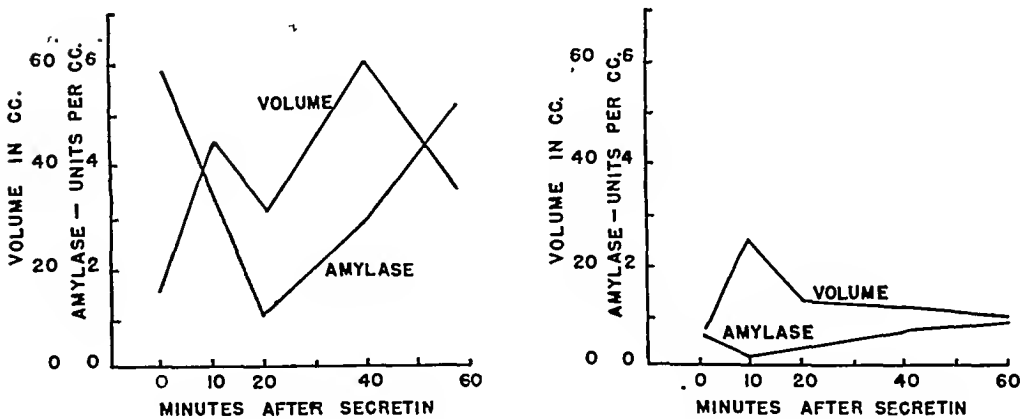


FIG. 2.—Quantitative evaluations of pancreatic functions.

apparently due to regeneration of the nerves.<sup>6</sup> Archibald first directly approached the problem by cutting the sphincter of Oddi in a human patient with recurrent pancreatitis.<sup>7</sup> He had noted the uniformly good results which followed removal of a stone impacted in the ampulla, when, perforce, the sphincter had to be cut.

Studies on patients with proven recurrent pancreatitis substantiate Archibald's contention that when a common passageway exists spasm of the

sphincter will produce the disease and sectioning of the sphincter will relieve the disease. The study here reported was conducted on the basis of the following concepts:

A. That serum amylase determinations during an attack will establish the diagnosis of acute pancreatitis (Fig. 1). In the absence of a rise in serum amylase the diagnosis is not necessarily excluded. With long standing disease and fibrosis or calcification of the gland there may be no rise in serum amylase or the level may be low.

B. That the intravenous administration of an assayed quantity of secretin will produce a flow of pancreatic juice which, when collected through a

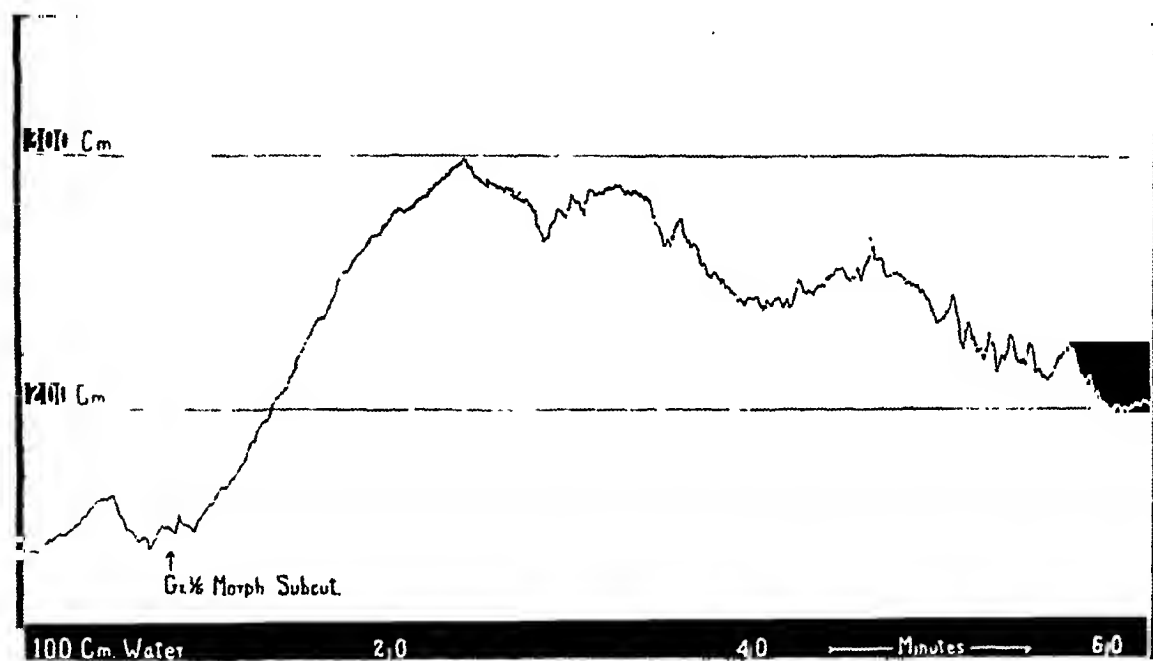


FIG. 3.—Effect of morphine on the sphincter of Oddi. Kymographic tracing of the resistance of the human sphincter of Oddi as measured through a T tube in the common duct, shows that the normal resistance of the sphincter (150 mm. of water) rises to 300 mm. and gradually subsides to 200 mm. in 1 hour. The effect persists for 4 hours.

duodenal tube, can be measured for total amount, amylase content, and bicarbonate content. The measurements are quantitative evaluations of pancreatic functions (Fig. 2).

C. That the administration of morphine will produce spasm of the duodenal wall and resistance to pancreatic and biliary flow, as demonstrated by kymographic pressure tracings recorded through a T tube in the common bile duct (Fig. 3). Cholangiograms done through a T tube in the common bile duct also demonstrate the contraction of the duodenal wall and resistance to the flow of bile (Fig. 4 & 5).

D. The N/10 Hydrochloric acid applied to the papilla of Vater will produce spasm of the sphincter of Oddi, as demonstrated by kymographic pressure tracings taken through a T tube in the common bile duct (Fig. 6), and in cholangiograms done through a T tube (Fig. 7). This same spasm can be

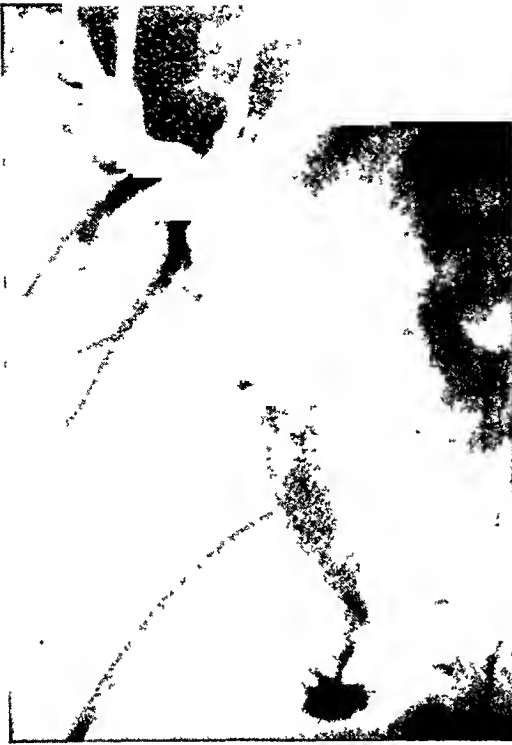


FIG. 4.



FIG. 5.

FIGS. 4 and 5.—A cholangiogram through a T tube 2 weeks after transduodenal sphincterotomy for ampullary stone, shows ready entrance of contrast medium into the duodenum (Fig. 4). Following administration of morphine (Fig. 5) the compression of the intramural portion of the common bile duct by the increased tonus of the duodenal wall is demonstrated.

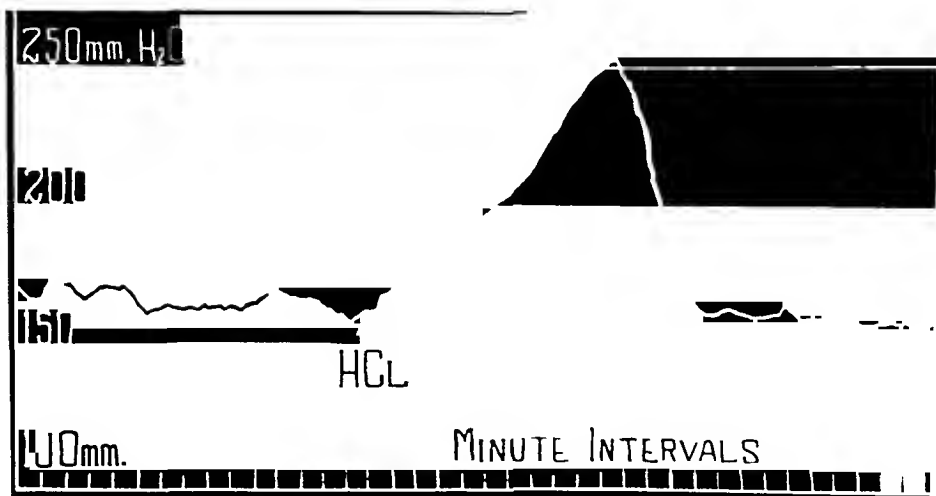


FIG. 6.—Kymographic tracing of the resistance of the sphincter as measured through a T tube in the common duct. The resistance of flow rises from 150 to 250 mm. of water. The effect lasts about 10 minutes.

produced by sudden, painful distension of the common duct through a T tube (Fig. 8 & 9).

E. That operative cholangiograms done by injecting contrast medium through a needle into the cystic or common duct at the same time that N/10



FIG. 7.—Cholangiogram performed through a cystic duct tube 2 weeks after cholecystectomy (sphincter intact). Hydrochloric acid applied directly to the papilla through a duodenal tube causes spasm and reflux of contrast medium into the pancreatic duct (arrow).

hydrochloric acid is applied to the papilla can demonstrate the passageway (Fig. 10).

F. That, after section of the sphincter muscle, the hydrochloric acid effect on the papilla is abolished (Fig. 11). The sphincter can no longer become spastic and biliary reflux under pressure is prevented. The morphine effect on the duodenal wall persists. Thus, reflux of the duodenal contents into the

biliary tract is prevented. In one patient with calcified pancreas and distortion of the duodenum and papilla, the muscle was incompletely sectioned as shown by kymographic tracings after hydrochloric acid application to the papilla (Fig. 12 & 13). This patient's pain was relieved, however, presumably because the resistance created by the remaining muscle fibers was insufficient to force bile into the pancreatic duct.

In patients whose pancreatic fibrosis is marked and pancreatic function diminished, sectioning of the sphincter relieves pain but does not restore normal digestion until the pancreas has regenerated which may take several weeks to months. (Fig. 14).

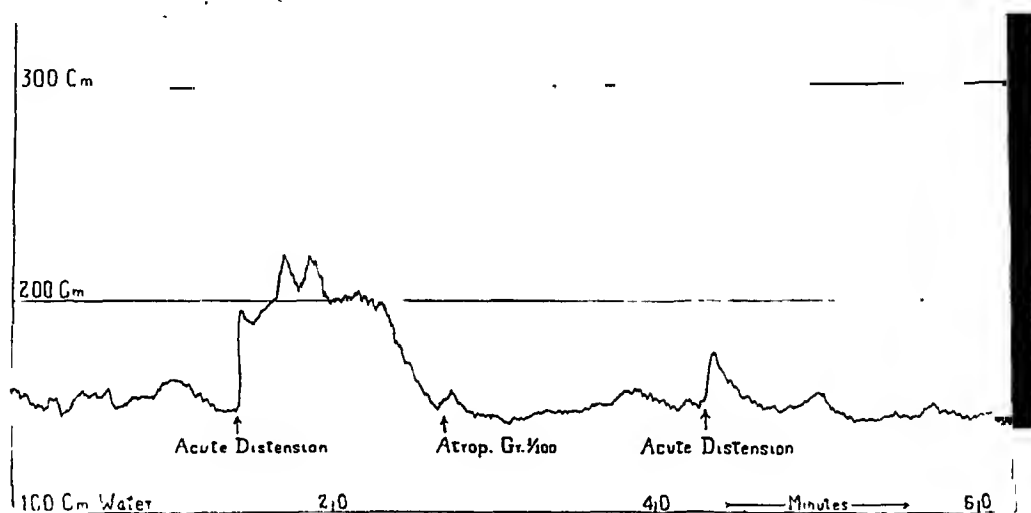


FIG. 8.—Effect of sudden distention of the common bile duct in the human through a cystic duct tube. Reflex spasm of the sphincter of Oddi raises the resistance to flow from 150 mm. to 225 mm. of water. The effect lasts about 10 minutes. Previous atropinization reduces this reflex spasm.

The actual sectioning of the sphincter is a somewhat exacting procedure. The papilla is difficult to find and when the muscle is in spasm the orifice may be extremely small. The best approach is through the common bile duct. An instrument\* described by Colp and Doubilet<sup>9</sup> for performing this operation without opening the duodenum has been used successfully in those patients whose sphincters are not in marked spasm or in whom there is no marked distortion or narrowing of the common duct. The duodenum may be opened over an instrument or over a probe. The muscle is then cut over the probe for about 1 cm. in the anterior free or intraluminal portion of the duct. The retraction of the sphincter muscle fibers prevents healing or regeneration of the muscle.

#### CASE SUMMARIES

**Case No. 1**—M.H. (Bellevue Hospital, No. 10199-47) was a 51-year-old female with a 22-year-old history of attacks of severe epigastric pain, lasting from 1 to 7 days, and increasing in frequency until they occurred every two weeks. In addition, there

\* Manufactured by The American Cystoscope Makers, New York, N. Y.

was almost daily transient epigastric pain after meals. Cholecystectomy was performed 20 years ago, and a choledochostomy and duodenostomy 7 years ago for an attack accompanied by jaundice. At that operation the jaundice was found to be due to a pancreatitis. She was admitted to Bellevue Hospital on February 24, 1947 during an attack of severe epigastric and left upper quadrant pain, associated with fever and paralytic ileus. At no time was the serum amylase elevated. The secretin test showed

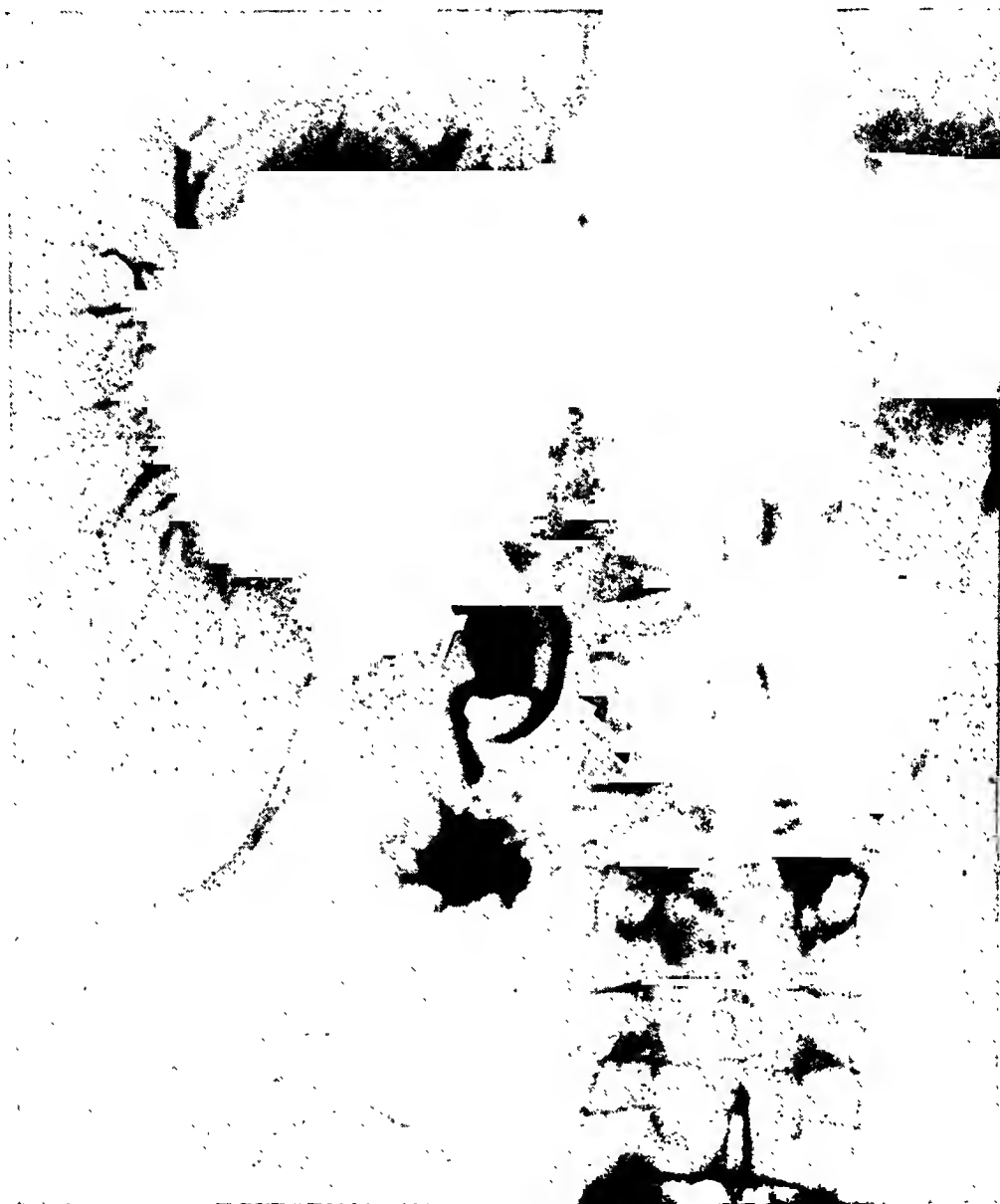


FIG. 9.—Cholangiogram performed through a T tube in the common duct. Sudden distention of the common duct by contrast medium causes pain and reflex spasm of the sphincter of Oddi. In this patient, due to a common passage, the contrast medium was forced up the main pancreatic duct (black arrow) and into the accessory pancreatic duct (white arrow) which can be seen to empty into the duodenum proximal to the papilla of Vater.

diminished function (total volume 104 cc; amylase 125 units). X-ray examination of the stomach and duodenum was reported normal.

At operation on March 24, 1947 the pancreas was uniformly enlarged and indurated. The common bile duct was moderately dilated. A cholangiogram showed pancreatic reflux when spasm of the sphincter of Oddi was induced by acid. Endo-



FIG. 10.—(Case 16) Operative cholangiogram in a patient with recurrent acute pancreatitis. Contrast medium injected through a needle in the cystic duct at the same time as hydrochloric acid was applied to the papilla of Vater through a duodenal tube, was forced into the pancreatic duct, visualizing it throughout its length. (arrow).

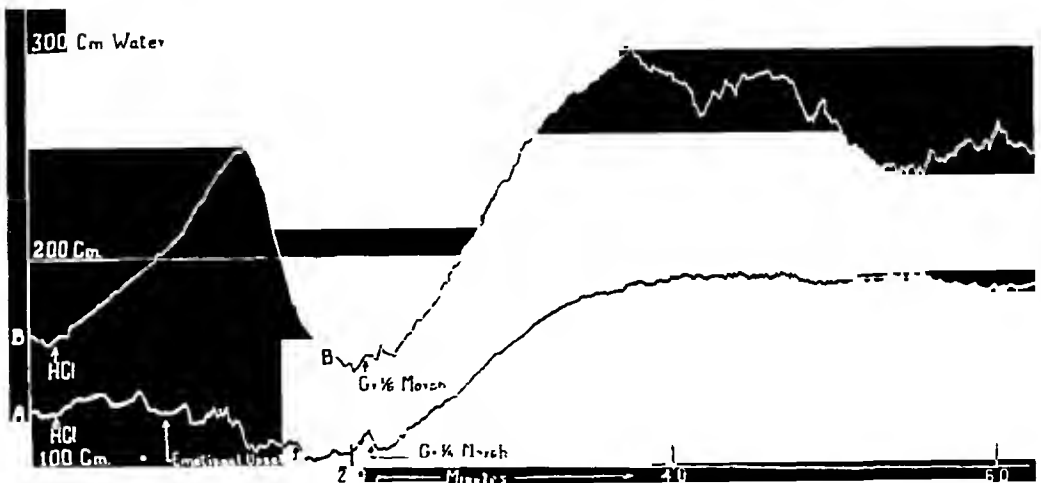


FIG. 11.—(Case 1) Kymographic tracing (A) recorded through a T tube in the common duct of the resistance to flow of bile into the duodenum in Case No. 1, indicates that the sphincter of Oddi is destroyed functionally since there is no response either to local application of acid or to emotional stimuli. The response to morphine is limited to its action on duodenal musculature. This tracing can be compared to the response of the intact sphincter to acid and morphine (B, superimposed).



FIG. 12.—(Case 15). Calcification of the pancreas.

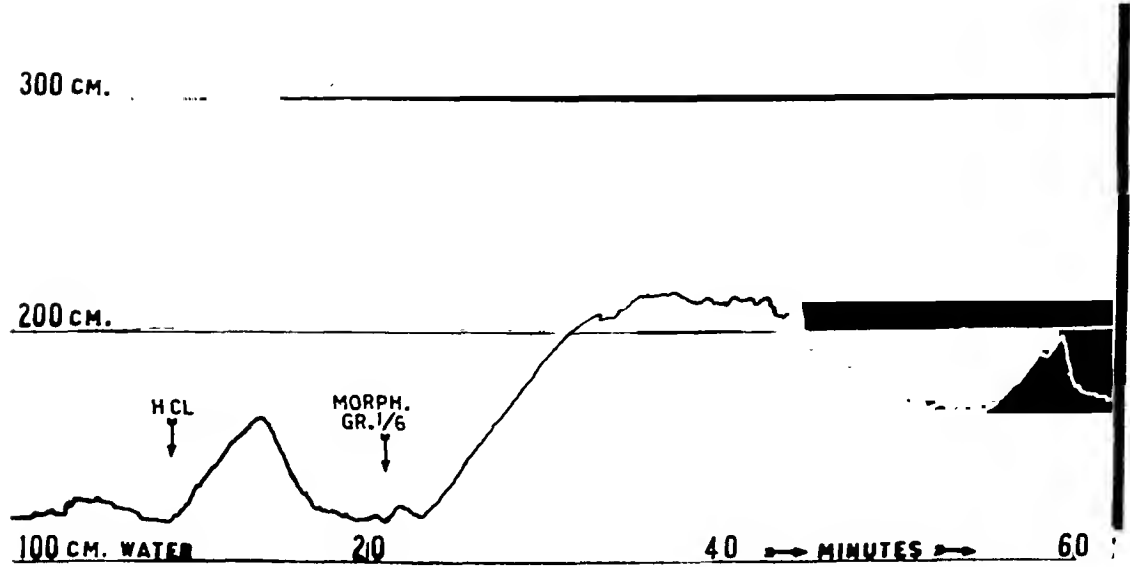


FIG. 13.—(Case 15). Kymographic tracing, recorded through a T tube in the common duct, of the resistance to flow of bile into the duodenum 2 weeks after sphincterotomy, reveals incomplete section of the sphincter of Oddi, since there is a mild response to hydrochloric acid. The response to morphine however, shows adequate destruction of the sphincter muscle.



choledochal sphincterotomy was performed and the common duct drained by a T tube. Two weeks after operation, cholangiographic studies using hydrochloric acid failed to visualize the pancreatic duct, (Fig. 15 and 16) but the use of morphine showed that the intact duodenal wall acted as a one way valve and prevented duodenal reflux. Kymographic studies supported these findings (Fig. 11). The patient has been asymptomatic since operation and has gained 18 pounds in weight.

**Case No. 2—L.N.** (Bellevue Hospital, No. 14276-47) was a 43-year-old female with a 20-year history of recurrent attacks of severe epigastric pain radiating to the back and to left upper quadrant. Investigations of her stomach, duodenum, esophagus, gall bladder, colon and kidneys were all negative except for gastric achlorhydria. A secretin test showed reduced function of the pancreas, (total volume 60 cc, total amylase 18 units). At operation on April 7, 1947, some adhesions around the gall bladder were found. The pancreas was normal to palpation. A cholangiogram failed to visualize the pancreatic duct. Cholecystectomy and endocholedochal sphincterotomy was done. Postoperatively, there was little drainage through the T tube, due to the fact that the distal part of the cross arm was twisted and occluded. A cholangiogram performed immediately after the removal of the T tube showed a narrowed, irregular common duct emptying readily into the duodenum. The pancreatic duct was not visualized.

The patient was well for 2 months, when she developed several attacks of transient epigastric pain lasting 5 minutes. Eight months after operation she had 2 attacks of severe epigastric pain after eating pork chops. At no time was the serum amylase found elevated. She had other complaints,—pain at the cardiac sphincter on drinking water, globus hystericus, urinary frequency. Sectioning of the sphincter in this patient was ill-advised.

**Case No. 3—J.S.** (Bellevue Hospital No. 18966-47) was a 57-year-old male with a 9-year history of recurrent attacks of severe epigastric pain radiating to the back and both scapulae, associated with marked gaseous distension and lasting on each occasion from 2 to 7 days. A cholecystectomy was performed in this hospital in 1939 for chronic non-calculus cholecystitis. After operation, he developed a wound dehiscence which was repaired. His attacks persisted but observations both on the ward and in the out-patient-department revealed no positive findings. The serum amylase was always low, never rising over 50 mg. %. A secretin test showed normal pancreatic function. By exclusion, a diagnosis of recurrent acute pancreatitis was made. At operation on May 29, 1947 very extensive adhesions of the stomach, duodenum, colon and liver were found. The common duct was very narrow, and the pancreas felt normal to palpation. A cholangiogram, using acid to produce spasm of the sphincter of Oddi, visualized the pancreatic duct. A probe was passed down the common bile duct into the duodenum, and after opening the duodenum, the sphincter was cut under vision. A fine catheter was passed down the common duct into the duodenum and brought out through the wound.

Postoperatively, his wound separated on the 3rd day and a biliary fistula developed, but after a stormy convalescence he was discharged with his wound healed. The patient was seen on the 18th of May, 1948. He had gained 50 pounds in weight; he had no pain; was eating without any restriction and is a completely rehabilitated person.

**Case No. 4—J.B.** (Bellevue Hospital, No. 26094-47) was a 47-year-old female, first admitted on September 17, 1945 with a 3-week history of recurrent attacks of severe epigastric and right upper quadrant pain, each attack lasting from 3 to 24 hours and accompanied by fever and leucocytosis. At that time a cholecystogram failed to visualize the gallbladder. She was discharged and observed in the out-patient-department. Roentgen ray studies of the stomach, duodenum and gall bladder showed no abnormality except for an irregularity in the duodenum. Typical attacks of pain

persisted. A diagnosis of recurrent acute pancreatitis was made but she was not admitted for operation until, during a very severe attack in May, 1947, the serum amylase was found to be 308 mg. %.

At operation, June 5, 1947, dense adhesions were present around the gall bladder and liver. The pancreas was moderately thickened. The gallbladder was thick and edematous and contained a few small stones. The common bile duct was moderately

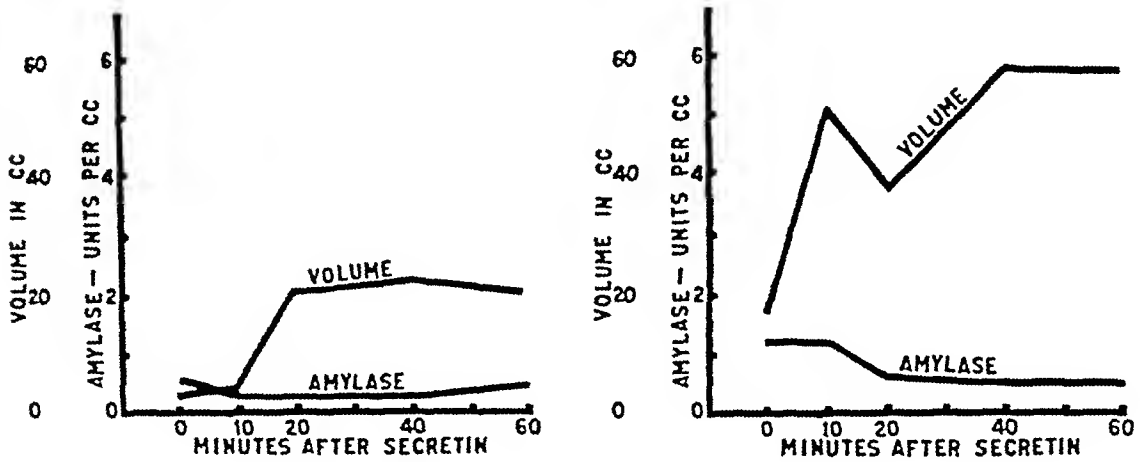


FIG. 14.—(Case 4).



FIG. 15.



FIG. 16.

FIGS. 15 and 16.—(Case 1.) Cholangiographic studies two weeks after sphincterotomy, shows the free entrance of contrast medium into the duodenum. (Fig. 15) Following application of acid to the duodenum (Fig. 16), the pancreatic duct is not visualized. Under similar conditions prior to sphincterotomy the pancreatic duct was visualized (Fig. 14.)

dilated. Cholangiographic studies showed that the bile and the pancreatic ducts emptied into a common ampulla a considerable distance from the ampulla of Vater (Fig. 17 and 18). Cholecystectomy and endocholedochal sphincterotomy were carried out. Histologic examination of the gall bladder showed acute and chronic cholecystitis. Biopsy of the pancreas revealed mild fibrosis. Two weeks after operation cholangiographic studies visualized the pancreatic duct presumably due to the fact that the junction of

the two ducts was high in the duodenal musculature (Fig. 19). Following the administration of morphine, the intramural parts of the ducts were compressed by the increased tonus of the duodenum, and the pancreatic duct was no longer visualized (Fig. 19). The secretin test showed marked reduction in pancreatic function (Fig. 14). Kymographic tracings indicated functional destruction of the sphincter of Oddi.

Patient has been asymptomatic since operation except for one attack of mild epigastric distress lasting 10 minutes following the eating of pork sausage. She has gained 20 pounds in weight. A secretin test performed 6 month after operation revealed marked improvement in the pancreatic function (Fig. 14).



FIG. 17.



FIG. 18.

FIGS. 17 and 18.—(Case 4) Operative cholangiogram through the cystic duct. Contrast medium was injected at the same time as hydrochloric acid was applied to the papilla of Vater through a duodenal tube. The pancreatic duct (arrow) was visualized (Fig. 17). Another view (Fig. 18) demonstrated an ampulla (arrow) high in the duodenal wall into which both ducts emptied.

**Case No. 5**—W.B., (Bellevue Hospital No. 38441-47) was a 58-year-old male with a 3 months history of epigastric pain radiating to the right upper quadrant and back. This pain was made worse by eating fatty foods. The pain was continuous and superimposed were bouts of very severe pain, vomiting and gaseous distension. Roentgenograms of the stomach and duodenum were normal; gallbladder visualized faintly. At operation on August 18, 1947, the gallbladder, although thin-walled, was adherent by old and fresh adhesions to the omentum, colon and duodenum. No stones were present. The pancreas felt normal. A cholangiogram through the common duct visualized the pancreatic duct (spasm of the sphincter of Oddi produced by hydrochloric acid). On the basis of the dense adhesions and the absence of stones, and the presence of the common passageway, a diagnosis of recurrent pancreatitis was made and the sphincter of Oddi was cut through the common duct. Histologic examination of the gallbladder showed minimal chronic cholecystitis. A cholangiogram 2 weeks after operation did not visualize the pancreatic duct in spite of injection of acid into the duodenum. A kymographic tracing revealed proof of the destruction of the sphincter of Oddi. The secretin test revealed normal pancreatic secretion (total volume 172 cc., total amylase 567 units). Since discharge, the patient has had a feel-

ing of epigastric pressure whenever he is constipated, but no persistent pain or acute attacks.

**Case No. 6**—M.W. (Bellevue Hospital, No. 40368-47) was a 32-year-old female who was admitted August 23rd, 1947 five days after onset of severe epigastric pain associated with vomiting. Similar attacks had occurred during the previous year. On admission, jaundice was noted (Icteric Index 15) as well as bile and a trace of sugar in the urine. Marked tenderness in the epigastrium and left upper quadrant were present. The serum amylase was 1355 mg. % on August 24th, 514 mg. % the next day, and 56 mg. % 5 days later. A cholecystogram on August 24, 1947 failed to visualize the gall bladder but on Sept. 4, 1947 repetition of the test showed good concentra-



FIG. 19.



FIG. 20.

FIGS. 19 and 20.—(Case 4) Cholangiogram done through a T-tube 2 weeks after operation. The pancreatic duct (arrow) was filled with contrast medium (Fig. 19) in spite of section of the sphincter because of an unusually high junction of the bile and pancreatic ducts. Morphine (gr. 1/6) increased the tonus of the whole duodenal wall and compressed the junction of the two ducts, preventing further reflux (Fig. 20).

tion and evacuation. Roentgenogram of the stomach and duodenum showed no abnormality. A secretin test showed normal pancreatic function (total volume 187 cc; total amylase 336 units). At operation on September 11, 1947 after separating adhesions around the liver, the gallbladder was found to be relatively normal; the common bile duct was twice the normal diameter; the pancreas was slightly indurated. A cholangiogram visualized the pancreatic duct. Cholecystectomy and endocholedochal sphincterotomy were performed. Cholangiography 2 weeks later performed through a T tube failed to visualize the pancreatic duct. Kymographic tracings of the resistance of the sphincter of Oddi indicated destruction of its function.

Patient seen on the 18th of May, 1948, gained 15 pounds in weight. Her complaint was that her increase in appetite and unrestricted diet was promoting too rapid gain in weight.

**Case No. 7**—G.B. (Bellevue Hospital, No. 46408-47) was a 43-year-old female with a 9-year history of recurrent attacks of moderate epigastric pain, lasting from  $\frac{1}{2}$  to 1 hour and relieved by vomiting. She had lost 15 pounds in weight because her food intake was restricted, since food brought on the attacks. Her gallbladder had

been removed at another hospital 13 years previously for cholelithiasis. She was admitted to this hospital on May 7, 1947, three days after a severe attack of epigastric pain radiating to the right upper quadrant, fever and vomiting. A serum amylase of 740 mg. % confirmed the diagnosis of acute pancreatitis. Roentgenogram of the stomach and duodenum revealed no abnormality. Patient was discharged and followed in the out-patient-department. Because of daily post-prandial pain and recurrent severe attacks, she was readmitted on October 2, 1947. A secretin test showed normal pancreatic function (total volume 185 cc; total amylase 367 units). At operation, the common bile duct was found moderately dilated; the pancreas firm but not enlarged; a hard mass was palpated in the lesser curvature of the stomach which was

opened; a small, deep gastric ulcer was found and excised. A cholangiogram failed to visualize the pancreatic duct, possible due to the fact that the end of the duodenal tube through which the acid was injected was not adjacent to the papilla. The common duct was opened and endocholedochal sphincterotomy performed. A cholangiogram performed 2 weeks after operation through the T tube visualized the pancreatic duct, (Fig. 21). A kymographic tracing, using acid and morphine, indicated destruction of the sphincter of Oddi.

The patient has been symptom free since operation.

Case No. 8—F.R. (Bellevue Hospital. No. 47498-47) was a 27-year-old female with a 3-year history of recurrent attacks of severe, mid-abdominal pain radiating to the epigastrium and left upper quadrant, occurring at varying intervals from daily to monthly, lasting from 2 hours to 1 week and accompanied by fever and tenderness in the epigastrium and left upper quadrant. Her last attack started 5 days before admission to the Third (New York University) Medical Division of Bellevue Hospital, October 9, 1947. Examination at this time revealed (1) jaundice (Icteric Index 22, bile in urine); (2) paralytic ileus (distended small bowel with fluid levels by



FIG. 21. — (Case 7) Cholangiogram through a T tube 2 weeks after sphincterotomy, visualized the pancreatic duct (arrow). As in Case 4, the high junction of the bile and pancreatic ducts permitted filling of the pancreatic duct in spite of sphincterotomy.

Roentgen ray); (3) diaphoresis with acidosis (blood sugar 250 mg. F, sugar and acetone in urine, carbon dioxide combining power in blood, 30 volume %); (4) hypertension (B.P. 158/96); (5) albumin in urine; (6) serum amylase over 300 mg. %.

Under treatment by intestinal suction, atropine, intravenous fluids and insulin all symptoms disappeared within 1 week. A cholecystogram 3 weeks after onset of attack visualized the gall bladder. Roentgenogram of the stomach and duodenum showed normal findings. The patient was transferred to the surgical service on November 1, 1947. A secretin test showed diminished pancreatic function (volume 91 cc.; amylase 92 units). At operation on November 7, 1947, a thin-walled gallbladder surrounded by dense adhesions was found; the pancreas was hard, enlarged to at least twice its normal size, and showed areas of old diffuse hemorrhage beneath its capsule. A cholangiogram visualized the pancreatic duct. The common bile duct was very narrow.

After cholecystectomy, the duet was opened and a fine probe passed into the duodenum, which was opened over the probe. The sphincter was sectioned and a fine catheter passed up the bile duct and out through the lateral angle of the wound. The duodenum was then closed. The catheter was dislodged accidentally on the 14th day and a cholangiogram, performed, immediately afterwards through the fistula, visualized the pancreatic duct (Fig. 22). The fistula closed the next day and the patient was discharged 16 days after operation. Histologic examination of a biopsy of the pancreas



FIG. 22.—(Case 8) Cholangiogram through a fistula two weeks after transduodenal sphincterotomy demonstrated a narrow common bile duct and filling of the pancreatic duct, due to its high entrance into the common duct.

showed a marked inflammatory reaction and replacement of acinar tissue by extensive fibrosis. She has been asymptomatic since operation, in spite of relapsing to old habits of periodic alcoholic sprecks. She has gained 20 pounds in weight.

Case No. 9—R.G. (Bellevue Hospital, No. 24620-47) was a 27-year-old female with a 4-year history of recurring attacks of epigastric pain radiating to the back and to both upper quadrants and lasting 10 to 30 minutes. Roentgenogram of the gallbladder showed a functioning viscus with stones. At operation on May 27, 1947, a moderately thickened gallbladder containing many stones was removed. A cholangiogram performed through the cystic duct visualized the pancreatic duct (Fig. 23 and

FIG. 23.



FIG. 24.

FIG. 25

FIGS 23, 24 and 25—(Case 9) Operative cholangiogram at first operation (cholecystectomy for chronic calculous cholecystitis) visualized a high junction of the pancreatic duct (arrow) with the common bile duct when the sphincter of Oddi was made spastic by acid (Fig 23). When the acid was washed away (Fig. 24) the pancreatic duct could not be visualized in spite of the continued injection of contrast medium. The relaxation of the duodenal wall was evident. A postoperative cholangiogram (Fig. 25) through a T-tube after the second operation (transduodenal sphincterotomy) again visualized the pancreatic duct (arrow), a common finding in the presence of a high junction of the bile and pancreatic ducts.

24). The cystic duct was then tied and the abdomen closed. The patient was discharged on the 9th postoperative day; that night she ate fried liver and was readmitted to the hospital during an attack of severe epigastric pain. The serum amylase was 595 mg. %. The symptoms subsided and 2 days later the serum amylase was 176 mg. %. She was discharged and followed in the out-patient-department. She remained well for 5 months and then increasingly severe attacks recurred. At re-operation on December



FIG. 26.—(Case 10). Operative cholangiogram through the cystic duct visualized the markedly dilated common bile duct and a dilated pancreatic duct (arrow). Spasm of the sphincter of Oddi was produced by acid applied to the papilla of Vater.

27, 1947, the sphincter of Oddi was cut transduodenally. A cholangiogram taken 2 weeks after operation visualized the pancreatic duct again (Fig. 25). Following administration of morphine, the pancreatic duct could no longer be visualized. Kymographic tracings indicated destruction of the sphincter of Oddi.

Since discharge from the hospital the patient complains of post-prandial pain lasting from 5 to 10 minutes, gradually decreasing in intensity. She is not symptom free as yet.

Case No. 10—A.W. (Bellevue Hospital, No. 387-48) was a 54-year-old female with an 8-year history of recurrent attacks of mid-abdominal and epigastric pain lasting from 1 to 3 days. She was admitted on December 6, 1947, three days after onset of a severe attack. The serum amylase was 382 mg. %, white blood count 18,000; the abdomen was distended and there was gas and fluid levels in the small bowel by Roentgen ray. There was also marked tenderness in the epigastrium and left upper quadrant. The symptoms disappeared in 2 days and the serum amylase



dropped to 75 mg. % 8 days after onset. The gallbladder failed to visualize, but radio-opaque stones could be seen. A secretin test revealed marked impairment of the pancreatic function (total volume 70 cc.; total amylase 235 units).

At operation, January 5, 1948, the colon, stomach and duodenum were found adherent to the gallbladder which was distended and full of small, black stones. The common bile duct was three times the normal size; the pancreas was firm but not unduly enlarged. Cholangiography visualized the pancreatic duct (Fig. 26). Cholecystectomy and endocholedochal sphincterotomy were performed. The patient de-

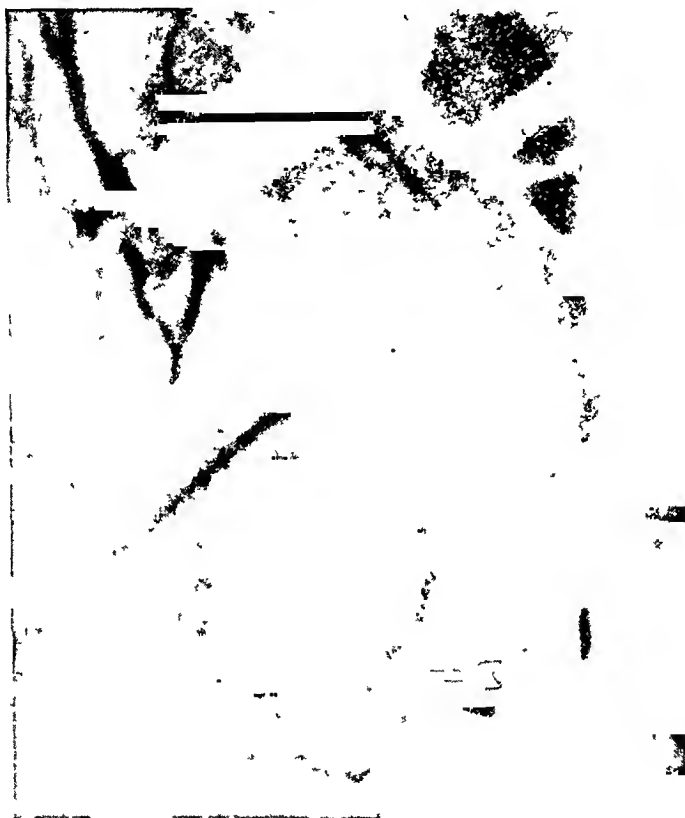


FIG. 27.—(Case 12). Postoperative cholangiogram through a T tube in the common bile duct visualized the pancreatic duct for a short distance with a primary branch (arrow). There was a dilatation of the portion of the duodenum proximal to the papilla with narrowing of the distal segment, possibly a factor in the pain this patient experienced after operation.

veloped shock-like symptoms during the operation which persisted with complete anuria until 3 days after operation when she died. The diagnosis of mismatched transfused blood was confirmed by histological examination of a section of the kidney.

Case No. 11.—H.W. (Bellevue Hospital, No. 906-48) was a 49-year-old white male, admitted on January 6, 1948. In 1940 a cholecystostomy had been performed for acute gangrenous cholecystitis with stones; the patient was well except for intolerance to fatty foods and post-prandial gaseous distension until November, 1947, when he began to suffer from attacks of very severe epigastric and right upper quadrant pain radiating to the back, often accompanied or followed by periods of frothy diarrhea. In between these attacks he had epigastric pain after almost every meal, and became afraid to eat.

A secretin test on January 6, 1948 revealed: marked impairment of pancreatic function (volume 40 cc., total amylase 88 units).

At operation on January 8, 1948, dense adhesions were found at the porta hepatis. The common duct was twice its normal size. The pancreas was enlarged and hard in its entire length. A cholangiogram showed a dilated common duct but failed to visualize the pancreatic duct; no evidence of the previously drained gallbladder could be seen. The common duct was opened and endocholechohal sphincterotomy performed. The common duct was closed and a small drain placed close to it. Convalescent was uneventful and attacks of pain ceased. He has had no diarrhea since

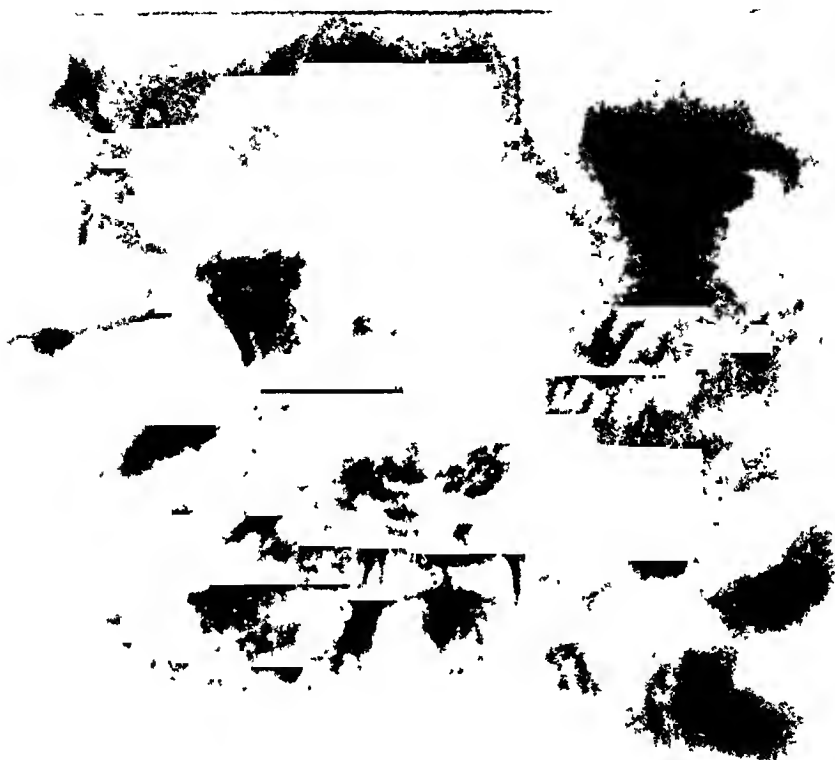


FIG. 28.—(Case 14). Operative cholangiogram through a needle in the cystic duct visualized the whole length of the pancreatic duct (arrows). The buicket of the duodenal tube through which acid was applied, can be seen lying against the papilla.

the operation. However, 3 months later he complained of a steady aching pain in the right side of the abdomen radiating across to the left side. Up to the present time, the cause of this pain has not been determined. A secretin test on May 12, 1948 showed marked improvement in pancreatic function (total volume 88 cc., total amylase 135 units.).

Case No. 12—M.L. (Bellevue Hospital, No. 659-48) was a 34-year-old female who had a chronically inflamed gall bladder with stones removed in 1941. The attacks of severe epigastric pain, radiating to the back and both upper quadrants from which she had suffered for 5 years prior to operation, recurred 9 months after operation and for 6 months had been so severe and so frequent as to incapacitate her. Under observation on the ward she developed 2 severe attacks of epigastric pain associated with marked tenderness in the upper left quadrant. The serum amylase was not elevated. A secretin test revealed normal pancreatic function (total volume 143 cc.; total amylase 497 units). Roentgenograms of the stomach and duodenum showed no abnormality. At operation, January 12, 1948 dense adhesions were found between the liver and the

stomach, duodenum and colon. The pancreas was not unduly indurated. The remnant of the cystic duct, 2" long, was isolated and removed. The common duct was dilated twice its normal size. A cholangiogram failed to visualize the pancreatic duct. The common duct was opened and the sphincterotome passed to the papilla, but it could not be pushed into the duodenum without undue force. The duodenum was opened and the papilla found tightly contracted. It was dilated and the sphincterotome pushed through under vision and the sphincter sectioned. The duodenum was closed and the common bile duct drained by a T tube. Cholangiographic studies 2 weeks later visualized the pancreatic duct, but showed marked narrowing of the duodenum



FIG. 29.



FIG. 30.

FIGS. 29 and 30.—(Case 14). Cholangiographic studies carried out through a T tube two weeks after sphincterotomy. Sudden painful distention of the common duct with contrast medium failed to produce spasm of the sphincter of visualization of the pancreatic duct (Fig. 29). After morphine injection the cholangiogram demonstrated compression of the terminal part of the common duct by the increased tone of the duodenal wall, showing that its one-way valve action was intact (Fig. 30).

with dilatation of the first part evidently as the result of opening the duodenum (Fig. 27). Kymographic studies indicated destruction of the sphincteric function.

Since operation, the patient has complained of attacks of transepigastric pain lasting from 5 to 10 minutes, and occurring after meals. When last seen she stated that the attacks have been decreasing in frequency and severity but she still had some tenderness on pressure in the epigastrium.

Case No. 13—D.C. (Bellevue Hospital, No. 43131-46) was a 38-year-old female, first admitted on September 10, 1946, 3 days after onset of an attack of acute pancreatitis associated with jaundice and serum amylase of 256 mg. %. The attack subsided rapidly but recurred following a fatty meal (Fig. 1). A cholecystogram failed to visualize the gall bladder, but several radio-opaque stones could be seen in the region of the common duct. At operation, October 3, 1946, a thick-walled gall bladder filled with stones was removed. The common bile duct was indurated, enlarged and contained 4 stones. A cholangiogram failed to visualize the pancreatic duct but the intravenous injection of secretin was followed by the appearance of pancreatic juice in the common duct, thus proving the presence of a common passageway. It was felt

that the pancreatitis was due to obstruction of the papilla of Vater by a stone and was not due to spasm. Accordingly, the sphincter of Oddi was not sectioned.

The patient was free of symptoms for one year when attacks of epigastric pain recurred and increased in frequency. Roentgenogram of the stomach and duodenum revealed no abnormality. Re-operation January 23, 1948 revealed 3 more stones in the common duct, apparently missed at the first operation. They caused no jaundice but



FIG. 31.—(Case 15). Operative cholangiogram through a needle in the cystic duct failed to visualize the pancreatic duct. The common bile duct was dilated and its retroduodenal course distorted by the calcified pancreas (Fig. 12).

possibly reflex spasm of the sphincter had resulted in recurrent attacks of pancreatitis. A cholangiogram revealed the pancreatic duct emptying into the ampulla low down near the papilla. Palpation of the stomach disclosed a thickening at the lesser curvature on the posterior wall. The stomach was opened and a large, shallow ulcer, 1.5 cm in diameter was seen. It appeared to be benign but a biopsy was taken to confirm this. The opening in the stomach was closed. Endocholedochal sphincterotomy was then performed. Two weeks after operation, a cholangiogram visualized the terminal part of the pancreatic duct. Kymographic studies indicated the destruction of the sphincter of Oddi. Biopsy of the gastric ulcer was reported a benign.

Roentgenological examination on May 11, 1948 revealed a defect in the gastric wall, which may be a persistent ulcer (although the patient has been well and gaining weight) or a recurrence.

**Case No. 14—O.T.** (Bellevue Hospital, No. 12709-47) was a 44-year-old male addicted to alcoholic sprees following which, during the past 3 years, he would develop very severe attacks of epigastric and right upper quadrant pain, abdominal distension and vomiting. He was admitted to a number of different hospitals for this condition but no accurate diagnosis was made until, during an admission to Bellevue Hospital in March, 1946, a diagnosis of recurrent acute pancreatitis was made on the basis of serum amylase determinations (Fig. 36). Roentgenogram of the gall bladder, stomach and duodenum showed no abnormality. He left the hospital when his symptoms subsided but, after several more attacks, returned for operation. A secretin test



FIG. 32.—(Case 19). The cholecystogram demonstrated a normal gallbladder and calcification in the head of the pancreas (arrow). The tube visible in this film lay in the pancreatic fistula to the skin.

showed normal pancreatic function (total volume 271 cc.; total amylase 638 units).

At operation on Feb. 11, 1948 dense adhesions were found between the liver and the adjacent organs. The gallbladder was thin-walled and contained no stones. The pancreas was firm. The common duct was normal in diameter. A cholangiogram visualized the whole pancreatic duct (Fig. 28). Cholecystectomy and endocholedochal sphincterotomy were performed. Cholangiographic studies 2 weeks after operation failed to visualize the pancreatic duct under spasm of the sphincter produced by pain (Fig. 29). After morphine administration, the function of the intact duodenal wall as a one-way valve could be seen to be intact (Fig. 30). Kymographic studies were further evidence of destruction of the sphincter of Oddi.

The patient had no further attacks of pancreatitis as observed during subsequent hospital admission for alcoholism.

**Case No. 15—F.J.** (Bellevue Hospital, No. 4485-48) was a 50-year-old male with a 13-year history of attacks of severe upper mid-abdominal pain, radiating to the epigastrium and left upper quadrant, lasting 2 hours to 2 days and occurring 2

to 3 times a month. These attacks followed a big meal and were most severe if food were taken after a prolonged alcoholic spree. There was no history of diarrhea. Roentgenograms of the abdomen revealed widespread calcification of the pancreas (Fig. 11); X-ray of the gall bladder showed normal visualization; and of the stomach and duodenum was reported as suggestive of duodenal ulcer. The glucose tolerance curve was normal. A secretin test showed diminished volume response of pancreatic juice flow but fairly good amylase concentration (total volume 105 cc.; total amylase 297 units). Since the symptoms were similar to those of non-calcified recurrent acute pancreatitis, and since he had good external and internal pancreatic function, it was decided to treat him as recurrent acute pancreatitis.

At operation, February 19, 1948, only a few adhesions were present at the fundus and ampulla of the gallbladder which was thin-walled. The pancreas was markedly enlarged throughout, very hard, and with cobble-stone-like surface. The head of the pancreas pushed the duodenum forward and distorted it. A thin scar on the anterior duodenal wall was suggestive of a healed duodenal ulcer. A cholangiogram showed an enlarged common bile duct with distortion due to pressure from the pancreas, but the pancreatic duct was not visualized (Fig. 31). The gallbladder was removed and the common duct opened. Due to difficulty in passing the sphincterotome through the papilla, the duodenum was opened and the instrument passed through under vision. The blade was then opened, retracted and the sphincter sectioned. Two weeks after operation, cholangiographic studies again failed to visualize the pancreatic duct. Kymographic studies showed a slight response to acid indicating possibly incomplete section of the sphincter but the response to morphine showed excellent functional destruction (Fig. 13). The patient has had no symptoms since operation but the acid test of an alcoholic bout has not yet been applied.

**Case No. 16—C.R.** (Bellevue Hospital, No. 7790-48) was a 29-year-old female with a 6-year history of recurrent monthly attacks of severe epigastric pain associated with nausea and vomiting, and radiating to both upper quadrants and to the back. Repeated Roentgenograms of the gallbladder, stomach and duodenum showed no abnormality. Exploratory laparotomy at another hospital during an acute attack in 1943 revealed acute pancreatitis. Cholecystostomy and drainage of the pancreas were performed. Drainage from the cholecystostomy site persisted intermittently for the intervening 5 years and, at one time during the course of this biliary drainage, a small cholesterol stone was extruded. When the fistula closed the attacks recurred.

She was admitted to this hospital on February 15, 1948. Contrast medium injection of the fistula revealed a small cavity which appeared to hold a radio-translucent stone. The drainage fluid contained no amylase. A secretin test showed marked reduction in the pancreatic function (total volume 42 cc.; total amylase 43 units). At operation on February 25, 1948, the fistula was found to communicate with a markedly fibrotic gallbladder containing a stone impacted in the cystic duct. The common bile duct was at least twice its normal size. The pancreas was hard throughout and moderately enlarged. A cholangiogram visualized the whole pancreatic duct (Fig. 10). Cholecystectomy and endocholechoal sphincterotomy were performed. The common duct was closed and a small drain, which was removed 4 days after operation, placed down to it.

Patient has been completely symptom free since operation.

**Case No. 17—J.D.** (Bellevue Hospital No. 8639-48) was a 32-year-old male with a 5-year history of frequent recurrent attacks of severe upper abdominal pain, sudden in onset, originating in peri-umbilical region and spreading up to the epigastrium and both upper quadrants and to back, accompanied by nausea and vomiting (bloody on 2 occasions) and lasting from 2 to 3 weeks. No diarrhea following these attacks. In November, 1946, a cholecystectomy was done but the attacks persisted. In 1947, at another hospital, a diagnosis of acute pancreatitis was made (serum amylase

FIG. 33.



FIG. 34.



FIG. 35.

FIGS. 33, 34 and 35.—(Case 19). Postoperative cholangiogram showed the catheter passing down the common bile duct into the duodenum (Fig. 33). Following partial withdrawal of catheter, the distorted narrowed common bile duct could be visualized (Fig. 34). A long thin shadow (arrow) to the right of the common duct might be the pancreatic duct but the distortion due to calcification of the head of the pancreas made this uncertain. Following administration of morphine (Fig. 35) the terminal part of the common duct was constricted by the increased tonus of the duodenal wall. The tube (arrow) lying in the pancreatico-gastrostomy was visualized.

281 mg. %) and confirmed by exploratory laparotomy. In February, 1948 a similar attack (amylase 209 mg. %) was observed. He was admitted to Bellevue Hospital February 19, 1948 at which time gastro-intestinal Roentgenologic findings were normal. Secretin test showed diminished function (total volume 132 cc.; total amylase 135 units). At operation on March 4, 1948, dense adhesions were found in the upper abdomen. The common duct was dilated 3 times its normal size; the pancreas was hard and enlarged throughout. An operative cholangiogram was unsatisfactory and failed to reveal the pancreatic duct. The common duct was opened and the sphincterotome passed. The duodenum was then opened and the sphincter of Oddi sectioned by the sphincterotomy under vision. The duodenum was closed and a T tube placed in the common duct.

Two weeks after operation a kymographic tracing showed evidence of destruction of the sphincter (no response to acid and diminished response to morphine). A cholangiogram showed ready entrance of contrast medium into the duodenum and failed to visualize the pancreatic duct. The T tube was removed on March 24, 1948 and the patient was discharged. He has had no symptoms since operation.

**Case No. 18—J.W.** (Holy Name Hospital, Teaneck, N. J., operation with Dr. Walter J. Farr) was a 53-year-old male with a 6-year history of attacks of right upper quadrant pain lasting 8 to 10 minutes. In 1944 a cholecystectomy was performed for stones. He was well for 6 months when extremely severe attacks in the right upper quadrant recurred, lasting from 10 minutes to 6 hours, and occurring 2 to 3 times a week. A diagnosis of recurrent acute pancreatitis was made. At operation, the pancreas was found to be enlarged and rock-like in consistency throughout its whole extent. The common bile duct was about 3 times its normal diameter with a thickened inflamed wall. Endocholedochal sphincterotomy was done and the common bile duct closed. A small rubber drain was placed down to the duct and removed 3 days later.

The patient has been free of symptoms since operation.

**Case No. 19—J.G.** (Bellevue Hospital, No. 906-48) was a 36-year-old male admitted to the psychiatric division of Bellevue Hospital on February 24, 1948 in a semi-stuporous condition due apparently to insulin hypoglycemia. He had a history of attacks of severe epigastric pain radiating to the back for 11 years. In 1940 an operation, cholecystostomy and drainage of a pancreatic cyst for obstructive jaundice due to the cyst, was performed. After 2 years the attacks of severe epigastric pain recurred and he became a morphine addict. In 1945, at another hospital, following studies which indicated marked diminution of pancreatic function, an attempt to do a pancreatectomy was abandoned and a splenectomy and drainage of a pancreatic cyst was carried out. He developed a persistent pancreatic fistula and attacks of epigastric pain persisted. After this operation a pancreatic-colic fistula was demonstrated but this apparently closed. At this time, the patient developed diabetes for which he required 40 Units of Insulin. He continued to have attacks of severe pain associated with paralytic ileus on occasion.

Studies at Bellevue Hospital revealed a severe diabetes (glucose tolerance curve: 173,235,333,308 mg. % sugar at  $\frac{1}{2}$  hour intervals). Injection of the pancreatic fistula visualized part of the pancreatic duct and showed free communication with the duodenum. Roentgenogram of the stomach and duodenum revealed a normal stomach with some obstruction of the duodenum. Secretin tests could not be done due to failure to pass a duodenal tube. Roentgen-ray studies revealed a normal functioning gallbladder as well as calcification in the head of the pancreas (Fig. 32). He required frequent injections of demerol for pain and to alleviate morphine withdrawal symptoms.

At operation on April 5, 1948 the stomach, duodenum and colon were found to be adherent to the liver. The gallbladder was surrounded by dense adhesions. The pancreatic fistula communicated with the body of the pancreas which was thickened and fibrosed with the head hard, irregular and enlarged. Many large veins coursed around



and over the gastrohepatic omentum, duodenum and pancreas. The common duct was located only after a cholangiogram was done through the cystic duct following removal of the gallbladder. The common duct was wide above and tortuous in its passage behind the head of the pancreas. The pancreatic duct was not visualized. The common duct was opened and a fine probe passed into the duodenum. The duodenum was opened and the sphincter of Oddi was cut transduodenally over the probe. A fine catheter was passed into the duodenum through the bile duct and brought out at the lateral angle of the wound. The pancreatic fistula was excised. The opening which remained in the main pancreatic duct was anastomosed to the overlying stomach over a small rubber tube. Cholangiograms taken 2 weeks after operation showed ready entrance of the contrast medium into the duodenum (Figs. 33 and 34). Following injection of morphine the duodenal musculature was shown to be intact (Fig. 35). Patient



FIG. 36.



FIG. 37.

FIGS. 36 and 37.—(Case 21). Calcification of the pancreas (Fig. 36) and operative cholangiogram through a needle in the cystic duct (Fig. 37). The angulation and narrowing of the bile duct in its passage behind the calcified head of the pancreas was noteworthy. A questionable shadow (arrow) may be the pancreatic duct.

has been asymptomatic since discharge, requiring no demerol and the pancreatic fistula has remained closed.

**Case No. 20.**—D.P. (French Hospital No. 138622) was a 31-year-old female with a 12-year history of attacks of epigastric pain radiating to the back over the 10th rib and to the left upper quadrant. The post-prandial pain has become so frequent that fear of eating led to a loss of 16 pounds in the last 6 months. Appendectomy was performed 12 years ago, and the removal of the right cystic ovary 6 years ago, without alleviating attacks. Complete physical and Roentgen-ray examinations at various hospitals failed to establish any diagnosis. A secretin test showed over 50% loss in pancreatic function (total volume 66 cc.; total amylase 325 units). On the basis of this test and the history, a diagnosis of recurrent acute pancreatitis was made. At operation on April 9, 1948, the gallbladder was found to be normal with only a few adhesions to the ampulla. The pancreas felt normal; the common bile duct was about twice its normal size. A cholangiogram was unsatisfactory owing to technical reasons. The gallbladder was removed and the common duct opened. The tip of the sphincterotome was arrested at the papilla and the duodenum was opened. The tip of the instrument was found arrested in a rather large ampulla of Vater due to the fact that the direc-

tion of the papilla was at right angles to the common duct. The instrument was pushed through the papilla and the sphincter of Oddi cut. When this was done the mouth of the pancreatic duct could be seen opening on the posterior wall of the ampulla 6 mm. above the papilla. A probe could be passed up the pancreatic duct for a distance of 8 cm. The common bile duct and the duodenum were closed and a small drainage tube placed down to that site; this was removed 3 days later. The patient has been asymptomatic since.

**Case No. 21**—D.R.W. (Beth Israel Hospital, Newark, N. J.—operation with Dr. A. Abrams) was a 40-year-old white male with a 12-year history of attacks of severe epigastric pain radiating to the back and to both upper quadrants, occasionally accompanied by vomiting. The attacks lasted from 2 hours to 2 days and at first occurred about every 6 months, but in the last few years the severe attacks occurred every few weeks and he had pain after eating almost every day. Ten years ago a diagnosis of perforated ulcer was made but no operation was done. Between 1940-1944 he was admitted to 4 different military hospitals. Many roentgenograms showed a normal gallbladder and normal stomach and duodenum. He was finally discharged from the army February 11, 1948 because of incapacitating pain. No diagnosis was made. Examination by a civilian physician revealed calcification of the pancreas (Fig. 36). A cholecystostomy was performed but by request of the patient the pancreas was not removed. He had no pain as long as the cholecystostomy was functioning. As soon as the drainage tube was removed the attacks of pain recurred. A secretin test done on April 12, 1948 revealed marked impairment of the pancreas (total volume 120 cc.; total amylase 65 units). At operation on April 16, 1948 the pancreas was found to be large and very hard with an irregular knobby surface. The gallbladder was removed. A cholangiogram visualized the pancreatic duct only questionably (Fig. 37). The common bile duct was about twice its normal size, and very tortuous, owing to its passage behind the enlarged irregular head of the pancreas. The common duct was opened, the sphincterotome passed into the duodenum and sphincterotomy done. The common duct was sutured and a small drain placed down to the line of suture. He has been asymptomatic since operation.

## DISCUSSION

The definitive surgical attack on acute recurrent pancreatitis accepts as its basis that when a common passageway between bile and pancreatic ducts can be demonstrated this anatomic arrangement permits the inception of the disease. It may be possible for other unknown mechanisms, not involving bile in the pancreatic ducts, to cause inflammation of the gland. Pancreatitis occurs in mumps and possibly in other virus diseases. Unaltered bile in the pancreatic duct may be innocuous; the anatomic possibility may be present without reflux ever actually occurring. In this conception, there are these conditions necessary for the occurrence of an attack: a common passageway; bile which has been rendered noxious by concentration of its salts or some other change; and spasm of the sphincter of Oddi.

A common passageway can be demonstrated by operative cholangiography or the presence of pancreatic juice in the gallbladder or common duct. That bile which is concentrated by the gallbladder is a likely chemical agent which is injurious to the pancreas is in part attested by the fact that cholecystectomy is frequently a temporary relieving measure.<sup>4, 10, 11</sup> The history of patients may reveal a period of freedom from pain after removal of a functioning

gallbladder without stones. Eventually, however, in some of these patients pancreatitis will occur. The sphincter of Oddi is the sealing mechanism which raises the pressure in the common system by recurrent spasm. This spasm can be induced by hydrochloric acid applied to the papilla. As with other muscular elements of the upper gastro-intestinal tract the contraction of the sphincter muscle is also controlled by nervous influences and possibly by hormones. Emotional disturbance or pain can induce spasm. In this sense dysfunction may be related to a similar dysfunction resulting in peptic ulcer or pylorospasm.

An unsolved aspect of this problem is how the bile can enter the pancreatic duct against the secretory pressure of the pancreas itself. Under the stimulus of secretin the flow of pancreatic juice will not permit bile to enter the pancreatic duct. Under the stimulus of ingested food bile pressure and pancreatic juice pressure are the same.

#### SUMMARY

Methods of diagnosis of recurrent pancreatitis by serum amylase determinations, pancreatic response to secretin stimulation, cholangiograms and biliary tract pressure recordings have been discussed. The etiologic factors first suggested by Archibald of spasm of the sphincter of Oddi in the presence of a common biliary-pancreatic passageway and reflux of bile into the pancreas have been studied on human patients. A summary of patients so studied and treated is presented. These studies confirm Archibald's opinions.

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DISCUSSION.—DR. HENRY DOUBILET, New York: I want to thank the members of the Association for the great honor and privilege of the floor. There are two points I should like to make. One is that this series of patients who have been operated on, forms only a small number of the total patients studied. In all routine biliary tract surgery a cholangiogram is done on the operating table. During this procedure normal tenth hydrocholic acid is applied to the papilla of Vater to produce spasm. These cholangiograms are valuable not only for the detection of common duct stones or malignancy, but also to determine the incidence of a common passageway and a reflux mechanism. A large proportion of these patients have been found to have a common passageway. Three of the patients in whom reflux mechanism was

demonstrated by operative cholangiography, since developed recurrent acute pancreatitis. One of these patients had a severe attack nine days after discharge, with an elevated serum amylase. She was finally readmitted and operated upon, at which time the sphincter of Oddi was cut. The other two patients are being followed in the outpatient department until such time as we can find an elevated serum amylase during one of their attacks.

The second point that is of great interest to us, is the relation of the reflux mechanism to the etiology of acute necrotizing cholecystitis or cholangitis with or without stones. The presence of pancreatic enzymes in the gallbladder or in the common duct is proof of reflux in these patients. We hope to have adequate studies in a few years to support a planned surgical approach in the therapy of these patients; that is, section of the sphincter of Oddi to prevent reflux.

DR. ALTON OCHSNER, New Orleans: This work is indeed stimulating. I regret that Dr. Gage is not here to discuss it because, as you know, he has been interested in the treatment of acute pancreatitis by sympathetic block, and I would like to give you some of the results on his cases, and also raise the question of whether in these acute recurrent pancreatitis attacks, in which Dr. Mulholland has shown that section of the ampulla has so dramatically relieved them—it would not be better to perform a plastic procedure on the duct rather than trans-choledochal section. Only time will tell whether this will give rise to stricture later. We have had two patients in whom we have done plastics on the duct, making an incision transductally and then suturing the ductal mucosa to the duodenal mucosa.

(slides) In the 15 cases Dr. Gage has had, typical splanchnic block has been done, using the Kappis technic. This technic consists of choosing a point 7 cm. lateral to the 12th spinous process at the lower border of the 12th rib. The needle is introduced at an angle of 45° until it strikes the body of the vertebra. The direction of the needle is slightly changed so that it can slide just beyond the body of the vertebra. The point of the needle lies in the retroperitoneal space where 15 cc. of ½ to 1 per cent novocain are injected on each side; two similar points are chosen 7 cm. caudad to the first two points and needles are similarly introduced. In all, four injections are made.

Dr. Gage is of the opinion that acute pancreatitis usually occurs when the choledochus and pancreatic duct open conjointly into the ampulla of Vater and that, as a result of obstruction of the communal duct, either by stone or spasm, reflux of bile into the pancreatic duct can occur which may produce acute pancreatitis by activation of the tryptic ferment and also by causing rupture of the pancreatic acini because of the markedly increased pressure within the pancreatic ducts. Because of the extensive fat necrosis associated with acute pancreatitis there is considerable demand for calcium to saponify the fat which results in decrease in blood calcium. For this reason, Dr. Gage is of the opinion that patients with acute pancreatitis should be given calcium intravenously. The hypocalcemia does not occur immediately after the attack but is most marked approximately a week after the onset of acute illness. Penicillin is given in order to prevent infection of the necrotic areas.

DR. H. F. GRAHAM, Brooklyn: I should like to comment on the papers of Dr. Cole and Dr. Mulholland. You will recollect that Dr. Cole mentioned that in about 25 per cent of cases they were not postoperative strictures according to his analysis. Dr. Mulholland mentioned the reflux from the biliary tract into the pancreas, and Dr. Doubilet has also shown that their studies have proved there is a reflux of pancreatic juice into the biliary tract. The cases that follow operation are tragic and distressing, but they are also controversial and subject to differences of opinion. We know of one case, however, an adult who had not been jaundiced previously, which eliminated the congenital aspect. He developed a chronic jaundice without previous

operation, was operated upon and complete obliteration of the common duct and the duct into the liver was found. It is going to be more difficult to prove that these cases are due to reflux of pancreatic juice than in the cases Dr. Mulholland demonstrated as due to reflux of bile, but I think some day this explanation will be accepted as the only rational explanation of many cases of stricture that occur. That can be determined usually by the extent of the stricture, which is much longer than the strictures found from operative interference. The upper end of the common duct is usually dilated after operative damage, while in these cases it is not.

DR. EVARTS GRAHAM, St. Louis: How long after cutting the sphincter does the paralysis last?

DR. JOHN H. MULHOLLAND, New York (closing): In reply to Dr. Ochsner's suggestion that a plastic operation on the sphincter mechanism might be advisable, I think it is vital to preserve the oblique passage of the common bile duct in the duodenal wall. The muscular intestinal wall containing the intramural portion of the common duct acts as a sphincter and is an effective bar to the reflux of duodenal contents in the biliary tract. None of these patients have developed cholangitis.

In answer to Dr. Graham, we know that our oldest patient, 18 months post-operative, has no evidence of sphincter spasm. Dr. Doubilet, who has done the basic experimental work concerned in this problem, has sacrificed dogs two years after the sphincter was cut and found it retracted and incompetent.

# OBSERVATIONS ON SOME METABOLIC CHANGES AFTER TOTAL PANCREATODUODENECTOMY\*

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EXPERIENCE WITH TOTAL PANCREATECTOMY has been too meager to allow a judgment of the ultimate usefulness of this procedure. Nevertheless, two statements concerning its future may fairly be made, namely, that the operation is a theoretically sound and promising one, and that its technical difficulties in themselves will not be an insurmountable obstacle to its wider popularity. Indeed, the factor that will most likely decide the fate of this procedure will be our ability or inability to learn to deal satisfactorily with the complex problems that arise in the postoperative management of the patients who have been subjected to it.

Total pancreatectomy is unlike other surgical procedures of similar magnitude in that it brings about profound changes in the physiologic processes of the human organism—changes that, unless they are corrected, are inherently progressive and fatal. In spite of the many valuable lessons learned from animal experimentation, our understanding of the physiologic behavior of the patient recently deprived of his pancreas is quite incomplete. An inadequate grasp of the problem of altered physiological response after total pancreatectomy has undoubtedly been the cause of many fatalities. This certainly has been the case in our experience. Conversely, an increase in the survival rate and a broadening of the usefulness of the operation will eventually come from a more thorough comprehension of the manner in which the human organism responds to removal of the pancreas.

Among the 17 cases of total pancreatoduodenectomy mentioned in medical literature<sup>1-12</sup> only seven lived long enough to allow postoperative investigations. Six of these have been described in detailed accounts by Priestly *et al.*,<sup>2</sup> Brunschwig *et al.*,<sup>3, 6, 7, 8</sup> Whipple,<sup>9</sup> Waugh *et al.*,<sup>10</sup> Dixon *et al.*,<sup>11</sup> and Clagett.<sup>10</sup> The report by Dixon, Comfort, Lichtman and Benson on the metabolic changes in a case of total pancreatectomy is unrivalled for thoroughness and richness of information.

In the present study certain observations on the postoperative course of three cases of total pancreatoduodenectomy of relatively long survival will be reported. These cases have not been described before, although Case 1 has been briefly referred to by McClure.<sup>4</sup>

## SHORT SUMMARIES OF THE CLINICAL HISTORIES

For better evaluation of the data to be presented, brief summaries of the clinical histories of the three cases will be first given.

**Case 1.**—(M.A.S. Case No. 76,836). Male, aged 43 yrs.—Admitted on January 2, 1944, with the complaint of intermittent griping distress across the mid-abdomen

\* Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

of two weeks' duration. Ease of fatigue, loss of appetite and loss of 20 lbs. of weight during the 8 weeks before admission. Clay-colored stool and dark urine for five weeks. Negative past and systemic histories.

*Physical examination:* Comfortable. Nutritional state fair. Markedly icteric. T.P.R. normal. B.P. 110/80. Liver palpable 6 cm. below the rt. costal margin, smooth and slightly tender. Gall bladder not palpable. The remainder of the examination essentially negative.

*Laboratory findings:* Kline exclusion test: negative. Urinalysis: positive for bile, otherwise negative. Routine and warm-stage stool examination: bulky and containing undigested meat; bile present; otherwise negative. The rest of the data of interest are listed in Table I. *Biliary drainage:* no B-bile; cholesterol crystals and clumps of w.b.c. *Roentgen-ray studies:* Serial films of the stomach and barium enema film: negative.

*Hospital Course:* Diagnosis: Obstructive jaundice caused by carcinoma of the head of the pancreas. *Operation (January 14 1944):* Total pancreatoduodenectomy; splenectomy; gastrojejunostomy and choledochojejunostomy. *Pathologic diagnosis:* Duct carcinoma of the pancreas, G. 2. *Postoperative recovery:* persistence of jaundice, some delay in emptying of the stomach and development of anasarca of moderate degree; slow but steady improvement. Discharged on the 23rd postoperative day in good general condition, weighing 137 lbs, on a diet of carbohydrates 200 Gm., protein 120 Gm. and fat 60 Gm., and on a daily medication consisting of pancreatin (U.S.P.) 3.0 Gm., protamine zinc insulin, 26 U., regular insulin p.r.n. and preparations of vitamin B, C and K.

*Course after discharge:* From February 6 to April 23 seen at weekly and bi-weekly intervals in the out-patient clinic. Symptom-free. Diabetes under satisfactory control with 26 to 28 U of protamine zinc insulin. Between April 23 and 30, 1944, admitted for studies. (Results shown in Table II.) From April 30, 1944 until November 11, 1944, seen at bi-monthly intervals. During this time, symptom-free; body weight 130-135 lbs.; diet on September 5, 1944, changed to C. 300, P. 135, F. 100; insulin increased to 40 U. protamine zinc insulin per day. One or two normal stools daily; 0.32 Gm. pancreatin (U.S.P.) t.i.d.; carrying on half-time work as salesman. On November 11, 1944, patient admitted with the complaint of intermittent low-abdominal cramps of a few days' duration; physical examination negative. Serial roentgen-ray films of the small bowel: pressure defects in the contour of stomach and duodenum probably due to extraneous tumor masses. *Diagnosis:* partial acute small bowel obstruction caused by metastatic carcinoma. After discharge on palliative medication on November 28, 1944, patient was lost sight of until March 10, 1945, when he returned with severe symptoms and signs of intestinal obstruction. He died on March 12, 1946, fourteen months after his pancreatectomy. An autopsy was performed, the important findings of which were as follows: Carcinoma of the pancreas (surgically removed). Metastatic carcinoma of the retroperitoneal lymph nodes, peritoneum and liver. Partial obstruction of jejunum by metastatic carcinoma. Peptic ulcer of jejunum at gastrojejunostomy. Small pulmonary emboli.

**Case 2.**—(A.S., Case No. 518,005). Female, aged 57 yrs.—Admitted on August 30, 1947, with the complaint of "yellow jaundice." Onset four weeks earlier of yellow color of skin, attacks of diarrhea with foul and bulky stools of light color associated with transient low-abdominal cramps. Loss of 38 lbs. of weight in four months. Diabetes of eight years' standing; poorly controlled with 24 U. of regular insulin daily. Hysterectomy in 1939.

*Physical examination:* comfortable, underweight, markedly jaundiced. T. 98.8, P. 78, R. 18. B.P. 120/70. Diabetic retinopathy, O.D. Liver palpable 4 cm. below right costal margin, gall bladder questionably palpable. Generalized arteriosclerosis.

TABLE I.—Preoperative Determinations of Hemoglobin, Erythrocytes, Leucocytes, Blood Chemistry, Icterus Index, Liver Function and Blood Enzymes.

	Case 1		Case 2		Case 3	
	Low	High	Low	High	Low	High
Hemoglobin, Gm. %						
Erythrocytes, million per cu. mm.						
Leucocytes, thousand per cu. mm.						
Blood sugar (fasting), mg. %						
CO <sub>2</sub> capacity, vol. %						
NPN, mg. %						
Chlorides, as NaCl, mg. %						
Albumin/Globulin, Gm. %						
Prothrombin, % normal						
Cholesterol, mg. %						
Cholesterol esters, % of total cholesterol						
Icterus Index, unit						
Bilirubin, direct, mg. %						
Bilirubin, total, mg. %						
LIVER FUNCTION TESTS						
Cephalin Cholesterol						
Thymol Turbidity, unit						
I Hippuric acid, oral, Gm.						
Alkaline Phosphatase, unit						
Lipase, unit						

NOTE: In this and the following tables the methods of determination were as follows: bilirubin, Malloy-Evelyn; bromsulphalein, Gaebler; calcium, Clark-Collip; CO<sub>2</sub>, Van Slyke (volumetric); chlorides, Whitehorn; cholesterol and cholesterol esters, Bloor-Knudsen; diastatic activity (amylase), Myers-Free-Rosinski; icterus index, Meulengracht-Brech; lipase, Cherry-Crandall; N.P.N., Folin-Wu; alkaline phosphatase, Bodansky; phosphates, Fiske-SubbaRow; potassium, Gaebler; albumin and globulin, Howe; prothrombin, Quick; sodium, Kramer-Gittelman; sugar, Folin-Wu (photoelectric); total fat, Bloor (oxidative); urea nitrogen, Van Slyke-Cullen; urinary nitrogen, Kjeldahl; stool nitrogen, Kjeldahl; blood acetone, Behre-Benedict; urinary acetone, Van Slyke.



TABLE II.—*Postoperative Determination of Blood Hemoglobin, Blood Chemistry, Icterus Index, Liver Function and Blood Enzymes.*

Case 1

TYPE OF DETERMINATION	POSTOPERATIVE DAY																POSTOPERATIVE WEEK		
	1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	12	40	65
Hemoglobin, Gm. %			10.5	10.0	10.0		9.0	9.0		9.0	7.9			11.0		11.0		13.9	
Sugar (fasting), mg. %	270	118	138	162		222	270	266	224	358	262	180		208	104	258		70	143
CO <sub>2</sub> Capacity, vol. %	47	53	67	74		67	85	70		47	59	46	45		54	53		63	
NPN, mg. %										35									
Chlorides, as NaCl, mg. %	457		427	435			400	493	445	457	453	493		480	487	413		38	
Total Protein, Gm. %								4.5				3.9		4.7				392	
Sodium, mg. %			331																
Phosphorus, mg. %							339		339	334		328		305	316	316		302	
Albumin/Globulin, Gm. %																			
Prothrombin, % normal											2.31							3.44	
Total Lipids, mg. %							20	45	100	100	2.25							4.16	
Cholesterol, mg. %					559	687	709	563	675	593	583			683	518	563		2.28	
Icterus Index, unit																		95	
Cephalin Cholesterol	78			102	98	96	80	69	32	55	36	26	26	25	25	23		450	390
Amylase, unit			4.0	3.0		2.3		8.5		10.0	8.7	4.3		3+				115	188
															6.4	9.6		1+	
																		11	

*Laboratory finding:* Data of interest are listed in Table I. *Biliary drainage* (Sept. 4, 1947): Bile not obtained. *Roentgen-ray studies:* Serial films of the stomach and duodenum (Sept. 8, 1947): negative.

*Hospital course:* Diagnosis: Obstructive jaundice probably caused by carcinoma of the head of the pancreas. Operation (Sept. 13, 1947): Total pancreatoduodenectomy. Gastrojejunostomy, choledocho-jejunostomy. *Pathologic diagnosis:* adenocarcinoma and fibrosis of the pancreas. *Postoperative course:* aside from a severe urethro-cystitis and a diarrhea, recovery rapid and complete. Discharged in good condition on October 5, 1947 (22nd postoperative day), on a diet of carbohydrate 250 Gm., protein 120 Gm., fat 70 Gm., and with the following medication: protamine zinc insulin 10 U. b.i.d., regular insulin p.r.n., pancreatin (U.S.P.) 75.0 Gm. daily and choline chloride 1.0 Gm. daily.

*Course after discharge:* From October 5, 1947 until November 11, 1947, patient seen once or twice weekly in the out-patient clinic. Only complaints: severe dysuria and urinary frequency. Diabetes under fairly good control with 25-30 U. of insulin. Poor home situation and patient obliged to do heavy housework soon after discharge from hospital; difficulty in maintaining weight. On November 24, 1947, admitted with signs and symptoms of acute intestinal obstruction of two days' duration. General condition on admission very poor. Surgery not attempted. Expired on November 27, 1947, eleven and a half weeks after her pancreatectomy. *Autopsy findings of importance:* Acute intestinal obstruction due to fibrous band arising from the bed of previously (1939) removed appendix; acute fibrino-purulent peritonitis; postoperative state following total pancreatoduodenectomy. Generalized arteriosclerosis. There was no evidence of any remnant or recurrence of the pancreatic carcinoma.

**Case 3.**—(L.T.S., Case No. 539,056). Female, aged 60 yrs. — Admitted on January 12, 1948, with the complaints of diarrhea and loss of 48 lbs. of weight in seven months. One month before admission onset of jaundice and appearance of diarrhea with large, greasy, light-colored stools. No pain, fever or chill. Attacks of gall bladder colic for a number of years. Known diabetic for 15 years with fairly good control on 25-30 daily U. of regular insulin. Seven months before admission B.M.R. plus 37; treated with Lugol's solution.

*Physical examination:* Evidence of recent weight loss. Markedly icteric. Comfortable. Temperature 98.6, pulse 90, respirations 18; blood pressure 150/80; weight 122 lbs. No exophthalmos or exophthalmic eye signs. Cardiovascular system essentially normal. Liver palpable 4 cm. below right costal margin. Gall bladder questionably palpable. The remainder of the findings unimportant.

*Laboratory findings:* The data of interest on blood determinations are listed in Table I. Kline exclusion serological test (January 12, 1948): negative. Urinalysis: positive Benedict test on repeated occasions, otherwise negative. Warm-stage stool examination and routine stool examination (January 13, 1948): absence of bile; undigested food elements, 4 plus guaiac. B.M.R. (January 20, 1948) plus 41, R.Q. 0.71; (January 24, 1948) plus 30. *Roentgenologic studies:* Barium enema examination of the colon (January 16, 1948): negative. *Cholecystograms* (January 14, 1948): non-function of the gall bladder, containing calcified gall stones. Serial films of the stomach (January 29, 1948): negative. *Biliary drainage* (January 14, 1948): no B-bile; suggestive evidence of gall stones and cholecystitis. *Duodenal drainage* (January 14, 1948): absence of pancreatic enzymes. *Gastric analysis* (January 14, 1948): fasting negative for free hydrochloric acid, all fractions containing free hydrochloric acid; chymification normal. *Electrocardiogram* (January 31, 1948): arteriosclerotic heart disease.

*Hospital course:* Diagnosis: Obstructive jaundice probably caused by carcinoma of the head of the pancreas. Operation (January 31, 1948): Total pancreatoduodenec-

TABLE III.—*Postoperative Determinations of Blood Hemoglobin, Blood Count, Blood Chemistry, Icterus Index and Liver Function.*

## Case 2

TYPE OF DETERMINATION	POSTOPERATIVE DAY														POSTOP. WEEK				
	1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	4	6	8
Hemoglobin, Gm. %	15.4	13.7	15.6	15.9	15.0	13.4	13.4		12.0	12.2	11.4	11.4	10.9	14.1					11.4
Erythrocytes, million/cu.mm.				4.9						4.4									
Leucocytes, thousand/cu.mm.	15.3	6.9	6.8	9.0	10.5	8.9	11.2		14.3	13.9	8.2	9.9	7.6	8.3					10.5
Sugar (fasting), mg. %	100	154	134	133	194	313	183	263	203	188	177	154	116	92	120		100	394	277
CO <sub>2</sub> Capacity, vol. %					67	91	93			66	57			56	58				
NPN, mg. %					43									37					
Chlorides, as NaCl, mg. %					340	373	373		420	427				477					
Albumin/Globulin, Gm. %									2.86 2.28	2.52 2.49				3.94 2.82					
Prothrombin, % normal					100									95					
Total Lipids, mg. %																			390
Cholesterol, mg. %																			134
Cholesterol Esters, % total Cholesterol						67													
Icterus Index, unit				57					31		26	23	18	19	18				
Cephalin Cholesterol					+									4+					
Thymol Turbidity, unit					1									2					
Thymol Flocculation					0									0					
Hippuric Acid, oral, Gm.														0.45					
Bromsulphalein, % re- tention/1 hr.																13			

tomy, splenectomy, choledochojejunostomy, gastrojejunostomy, cholecystostomy, removal of gall stones. *Pathologic diagnosis:* Adenocarcinoma of the pancreas arising in the duct system, G.2, with metastases to the regional lymph nodes. *Post-operative course:* Rapid and complete recovery in 14 days. Discharged after some metabolic studies on *February 23, 1948*. Discharge diet: carbohydrate 250 Gm., protein 150 Gm. and fat 100 Gm. Discharge medications: Pancreatin (U.S.P.) 1.32 Gm. t.i.d.; protamine zinc insulin 5 U. A.M. and P.M. with regular insulin p.r.n.; choline chloride 1.32 Gm. t.i.d.; propylthiouracil 50 mg. t.i.d.

*Course after discharge:* From *February 23, to March 14* patient was seen twice weekly in the out-patient clinic. Glycosuria difficult to control, daily 2 plus to 3 plus urinary sugar but no acetone. On *March 14, 1948* patient admitted for studies (see below). On *March 26, 1948*, patient was again dismissed; returned to her home 400 miles from Detroit under care of own physician. Medication: Pancreatin 8.0 Gm. daily; protamine zinc insulin 5 U. q.a.m., regular insulin p.r.n.; propylthiouracil 50 mg. t.i.d. On *April 26, 1948*, patient reentered the hospital for follow-up studies. At this time she felt well and complained only of occasional epigastric distress after eating. Physical examination showed no noteworthy abnormality other than moderate diabetic retinopathy, O.U. Temperature, pulse and respirations were normal; blood pressure 143/78; weight 115 lbs. The laboratory findings of interest are listed in Table IV. *Serial roentgenograms* of the upper gastro-intestinal tract (*April 27, 1948*): Some obstruction at the gastro-enterostomy stoma; visualization of the biliary tract with barium; otherwise negative. (Other studies in progress.)

#### IMMEDIATE POSTOPERATIVE OBSERVATIONS

In addition to the physiologic disturbances that follow any extensive and lengthy operation on the upper gastro-intestinal tract, the complete removal of the pancreas creates a special problem: that of a rapidly supervening diabetes; or if a state of diabetes already exists (as in our Cases 2 and 3), a temporary aggravation of the difficulties of controlling the diabetes.

The changes in carbohydrate metabolism and other physiologic processes were followed by daily determinations of the chemical constituents of the blood, the more important of which are listed in Tables II, III and IV and represented in Figures 2, 3 and 4. Blood sugar and CO<sub>2</sub> capacity often had to be determined two or more times daily because of the frequent unpredictability of their values.

During the first six to eight postoperative days the urine was collected in four daily batches and tested for glucose and acetone four times daily, each time of testing immediately preceding the next intravenous feeding. The insulin was administered in the intravenous fluid according to the results of the analysis of the urine and the blood glucose level.

The most significant and helpful data were the blood sugar, CO<sub>2</sub> capacity and chloride levels. In Cases 1 and 2, an alkalosis in terms of CO<sub>2</sub> capacity was observed: the CO<sub>2</sub> capacity rose as high as 94 vols. per cent. The explanation of this phenomenon is not easy to find. It has been suggested that the sudden cessation of the demand on the alkali reserve of the secretion of the highly alkaline pancreatic and duodenal juices may have set free untapped sources of alkali. In any case, the increase in CO<sub>2</sub> capacity had no deleterious effects and responded fairly well to treatment with medication supplying acid radicals.

TABLE IV.—*Postoperative Determinations of Blood Hemoglobin, Blood Count, Blood Chemistry, Icterus Index, Liver Function, Blood Enzymes, and Basal Metabolic Rate.*

## Case 3

TYPE OF DETERMINATION	POST OPERATIVE DAY													POSTOP. WEEK			
	1	2	3	4	5	6	7	8	9	10	12	14	16		18	20	22
Hemoglobin, Gm. %	12.7	11.5	11.5	11.1	12.4	10.3	11.7	11.7	13.1	13.4	13.1	13.6	12.2	12.0	11.7	10.7	13.6
Leucocytes, thousand/cu.mm.	17.6	19.3	17.0	15.4	13.2	16.1	16.7	15.8	22.1	12.5	12.4	10.7	12.3	10.2	14.0	13.3	13.7
Sugar (fasting), mg. %	167	61	180	175	156	154	151	100	207	85	206	320	85	72	59	200	
CO <sub>2</sub> Capacity, vol. %	48	55	60		67		60	58	59	41	57	41	52	52	40	56	40
NPN, mg. %										23	35	41	28		17	32	460
Chlorides, as NaCl, mg. %	463		400		420				440	460	440	320	380		514	420	364
Sodium, mg. %																	4.4
Phosphorus, mg. %																	9.0
Calcium, mg. %																	22.5
Potassium, mg. %																	4.64
Albumin/Globulin, Gm. %	3.84 1.85				3.28 1.74		2.82 1.88		3.68 1.64	3.00 2.50	2.85 2.17	2.63 2.29	2.95 1.85		3.82 2.60	2.74 2.04	1.96
Icterus Index, unit	45	39	45		32	31	26	27	26	15	18	16	20		16	12	
Prothrombin, % normal													72				
Total Lipids, mg. %	1020				838				645	562		532	533	570	613		593
Cholesterol, mg. %	450				410		427		178	286	194	208	235		164	200	210
Cholesterol Esters, % total															52	40	43
Bromsulphalein, % retention in 1 hour																	
Alk. Phosphatase, unit																	13
Hippuric Acid, oral, Gm.																	9.2
BMR, % above normal																	2.51
Lipase, unit	1.07		1.00		0.6				0.7	0.75		0.4	0.37			0.5	52
Amylase, unit	37		44		73		41		56	15			13		18	29	1.25
																	0

The blood chloride level was a valuable guide for the estimation of intravenous feedings. As one would expect, it showed no significant fluctuations as long as the intravenous therapy was adequate.

The behavior of the blood glucose values will be discussed below, as will also be that of the icterus index, blood lipids and blood lipase and amylase. The remaining blood chemical studies showed no characteristic alterations.

#### CARBOHYDRATE METABOLISM AFTER TOTAL PANCREATECTOMY

*Immediate postoperative period.*—As observed in our patients, two striking facts stand out in the immediate postoperative course of total surgical diabetes. First, the insulin requirement for maintaining a blood glucose level near the normal range is surprisingly low in comparison with the requirements of diabetes mellitus in which almost always a considerable amount of functioning island tissue is still present. As a corollary to this fact, the sensitivity to insulin of the depancreatized patient is much greater than that of the patient with diabetes mellitus. Our patients were satisfactorily controlled with from 10 to 60 units of insulin daily, the average number of daily units needed lying just around 30. On the other hand, we observed a severe insulin shock following the administration of 10 units of insulin three hours after a blood glucose level of 430 mg. per 100 cc. The second outstanding fact is the capricious behavior of the blood sugar. An effort was made to administer the intravenous fluids containing glucose at regular intervals in close correlation with the blood chemistry determinations and urine tests. It was not possible, however, to arrive at an entirely reliable scheme that would keep the urine persistently sugar-free yet not lower the blood sugar to a dangerous level. Some tentative explanations for this phenomenon will be offered presently.

Because of the insulin sensitivity and of the variability of the hyperglycemia of the depancreatized patient, we have endeavored to regulate the blood sugar level in the immediate postoperative period with the aim of keeping it well above rather than very near the normal range, that is, around 200 mg. per 100 cc. Either theoretically or as judged by practical experience, at least as a short-term type of management, this method has shown no untoward effects and has proved safe.

*Later postoperative period.*—The immediate postoperative period can be regarded as closed when the patient is well established on a satisfactory maintenance diet. In our cases this period extended from 14 to 23 days.

A rather trying space of time begins when the depancreatized patient starts taking food by mouth. Because of the inconstant appetite and poor digestion and absorption, the amount of actual food intake is hard to reckon and the control of the diabetes usually slips (cf. Fig. 1, 2 and 3).

After the patient has become well accustomed to his diet, a satisfactory control is not too difficult to attain. Given constant circumstances of dietary

intake, activity and health, the insulin requirement of the depancreatized patient does not vary widely. Case 1 lived a life of moderate activity in comfort for six months under good control of his diabetes with 26-28 units of protamine zinc insulin taken in the morning. Later his dosage rose to 40 units daily and toward the end of his life his control became difficult to maintain.

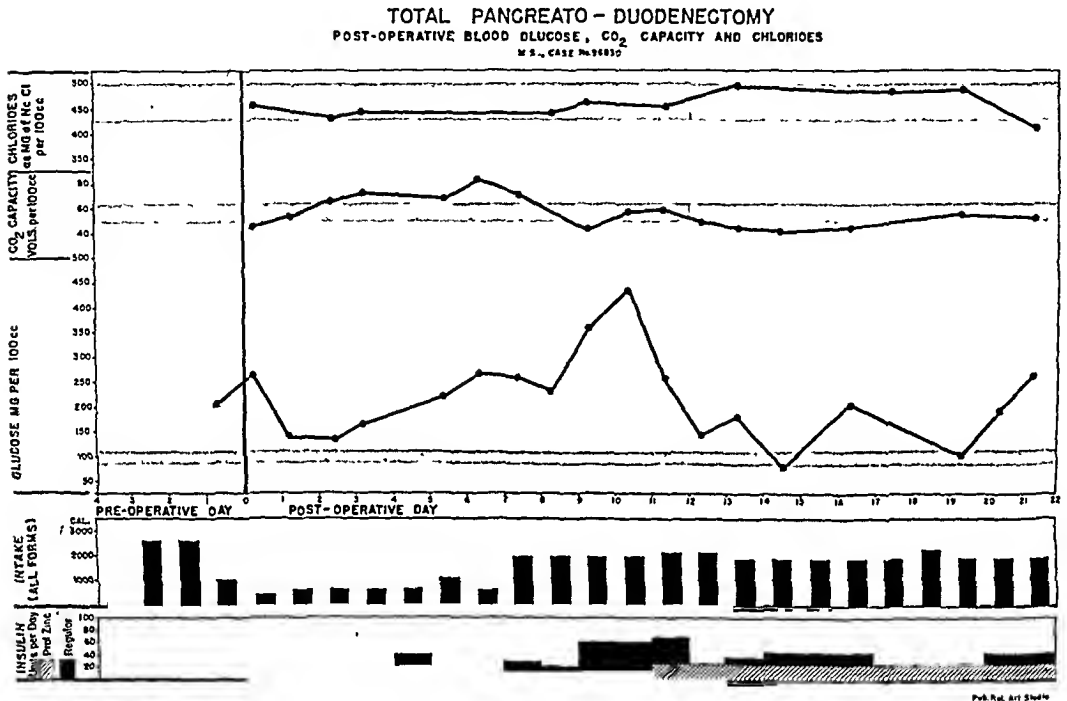


FIG. 1.—Case 1.—Postoperative changes in blood chlorides, CO<sub>2</sub> capacity and sugar. (Determinations on fasting blood specimens. Shaded bands for normal ranges of values.) — The figures for the total daily caloric intake represent calculated values. The average daily composition of the diet from which the caloric values were derived was fairly uniform for each of the following periods:—Last three preoperative days: carbohydrate, 350 Gm.; protein, 200 Gm.; fat, 50 Gm. First to sixth postoperative days: carbohydrate, 150 Gm.; protein, 35 Gm. Seventh to twenty-first postoperative days: carbohydrate, 200 Gm.; protein, 120 Gm.; fat, 50 Gm.

Changes in diet, bowel habits (diarrhea), and general health upset the control of these patients seemingly more readily than that of patients with diabetes mellitus. Case 2 was controlled in a satisfactory manner only for short periods of time on account of a recurrent urethro-cystitis of moderate severity. When in good health, her daily need was about 30 units; during the spells of illness this went up to 40 or 45 units. Control of the diabetes in Case 3 has been an especially difficult problem owing to the high basal metabolic rate (see below). Her daily requirement has been around 40 units. On this she feels well and maintains her weight but spills 2 to 3 plus sugar in her urine almost daily. A closer control in her case is dangerous since she has developed severe hypoglycemic shock (blood sugar 43 mg. per 100

cc.) upon the subcutaneous administration (by mistake) of 10 units of insulin four hours after a meal containing about 120 Gm. of glucose equivalent. The sensitivity to insulin, seen in an increased degree in this case, was not conspicuous in Case 1, but was quite evident in Case 2. This propensity made the use of protamine zinc insulin a matter of some risk in Case 3 and to a less extent in Case 2 also. Ten units of protamine

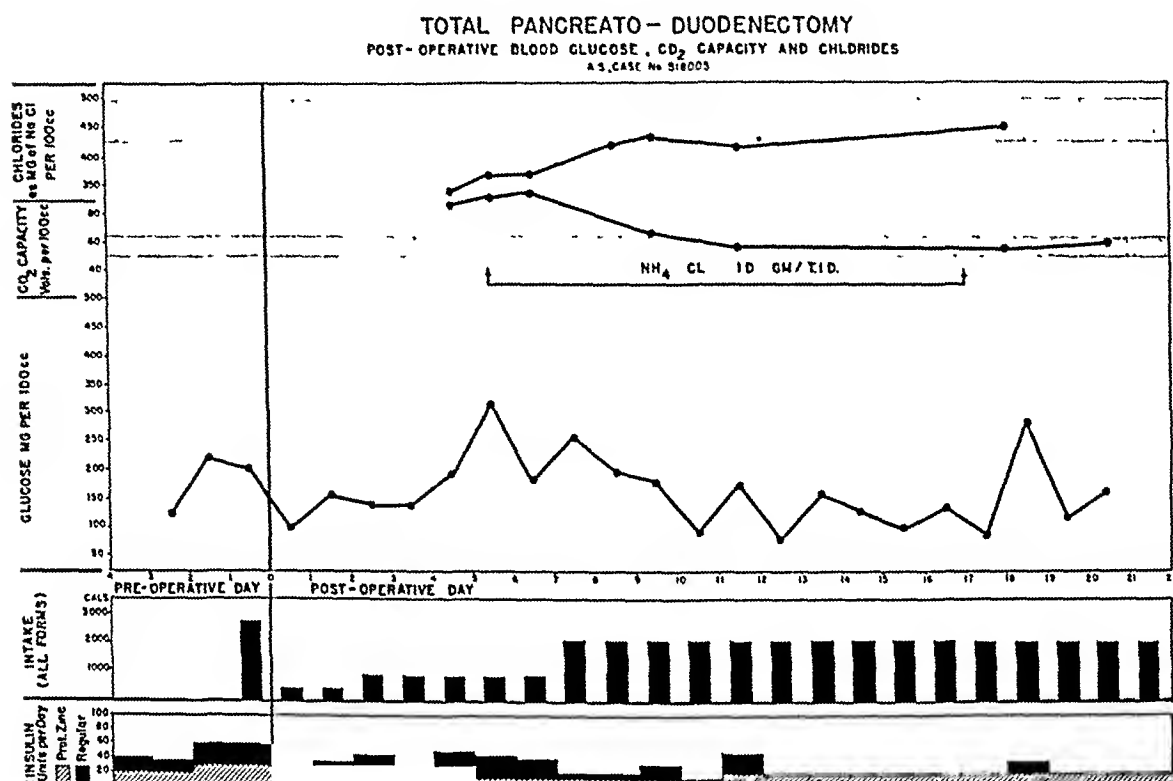


FIG. 2.—Case 2—Postoperative changes in blood chlorides, CO<sub>2</sub> capacity and sugar. (Determinations on fasting blood specimens. Shaded bands for normal ranges of values.) — The figures for the total daily caloric intake represent calculated values. The average daily composition of the diet from which the caloric values were derived was fairly uniform for each of the following periods. Preoperatively: carbohydrate, 350 Gm.; protein, 120 Gm.; fat, 70 Gm. First to sixth postoperative days: carbohydrate, 150 Gm.; protein, 125 Gm. Seventh to twenty-first postoperative days: carbohydrate, 250 Gm.; protein, 110 Gm.; fat, 80 Gm.

zinc insulin taken at 8 A.M. and 6 P.M. would on occasion cause a mild hypoglycemic reaction in the following morning, before the next injection, apparently by virtue of the summation of the effect of the two injections of the previous day. Case 3 became, for this reason, very antagonistic to the use of the long-lasting preparation. Nevertheless, whenever possible we attempt to administer about  $\frac{1}{2}$  to  $\frac{2}{3}$  of the daily insulin requirement in the form of protamine zinc insulin.

Because of the insulin sensitivity, we prefer to regulate the insulin dosage, also in the later postoperative period, in such a manner as to insure a fasting blood sugar on the hyperglycemic side (150 plus mg.).



The relatively low insulin requirement in total surgical diabetes has given occasion for much speculation. The basal insulin requirement of a totally depancreatized 60 kg. man has been estimated on the basis of calculations from animal experiments as 1.014 unit per hour or about 24 units per day.<sup>13</sup> If one increases this figure by 50 per cent to allow for the needs of the metabolic state for average activity the estimate of 36 units obtained is amazingly close to the average actually observed in our cases. From evidence such as this it has been suggested that in diabetes mellitus

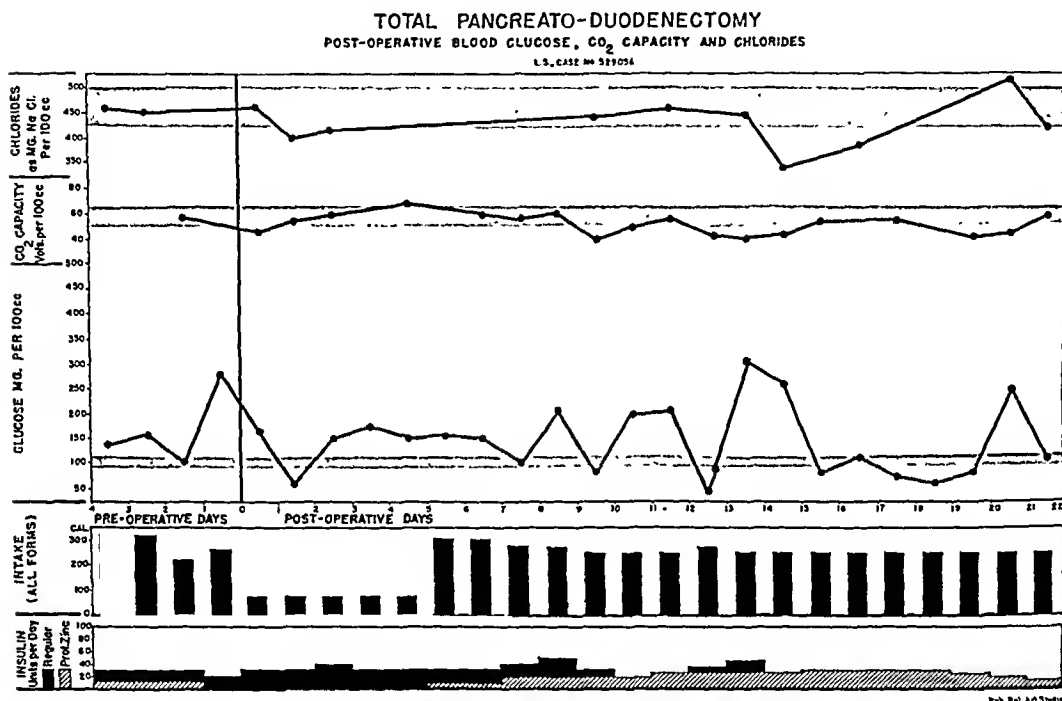


FIG. 3.—Case 3.—Postoperative changes in blood chlorides, CO<sub>2</sub> capacity and sugar. (Determinations on fasting blood specimens. Shaded bands for normal ranges of values.) — The figures for the total daily caloric intake represent calculated values. The average daily composition of the diet from which the caloric values were derived was fairly uniform for each of the following periods: Preoperatively: carbohydrate, 350 Gm.; protein 100 Gm.; fat, 60 Gm. First to four postoperative days: carbohydrate, 150 Gm.; protein, 50 Gm. Fifth to twenty-first postoperative days: carbohydrate, 250 Gm.; protein, 150 Gm.; fat, 100 Gm.

there is a factor at work that is absent in pure surgical diabetes. The recent work on the role of the pituitary and adrenal glands in the regulation of carbohydrate metabolism seems to favor such an assumption. In a recent laboratory experiment<sup>14</sup> the sequence of events observed in diabetic patients that underwent total pancreatectomy (Cases 2 and 3) has been duplicated to some extent. After diabetes of a determined severity had been produced in dogs by the administration of alloxan, total pancreatectomy decreased the degree of insulin requirement. The authors postulate

that there is a second pancreatic hormone generally antagonistic to insulin. It is possible that further observations on patients rendered diabetic surgically will shed light on these complex problems.

The seeming contradiction of the simultaneous presence of insulin sensitivity and tendency for hyperglycemia, and in particular the frequent un-

TOTAL PANCREATO-DUODENECTOMY:— SUGAR TOLERANCE CURVES

L.S., CASE No. 529056

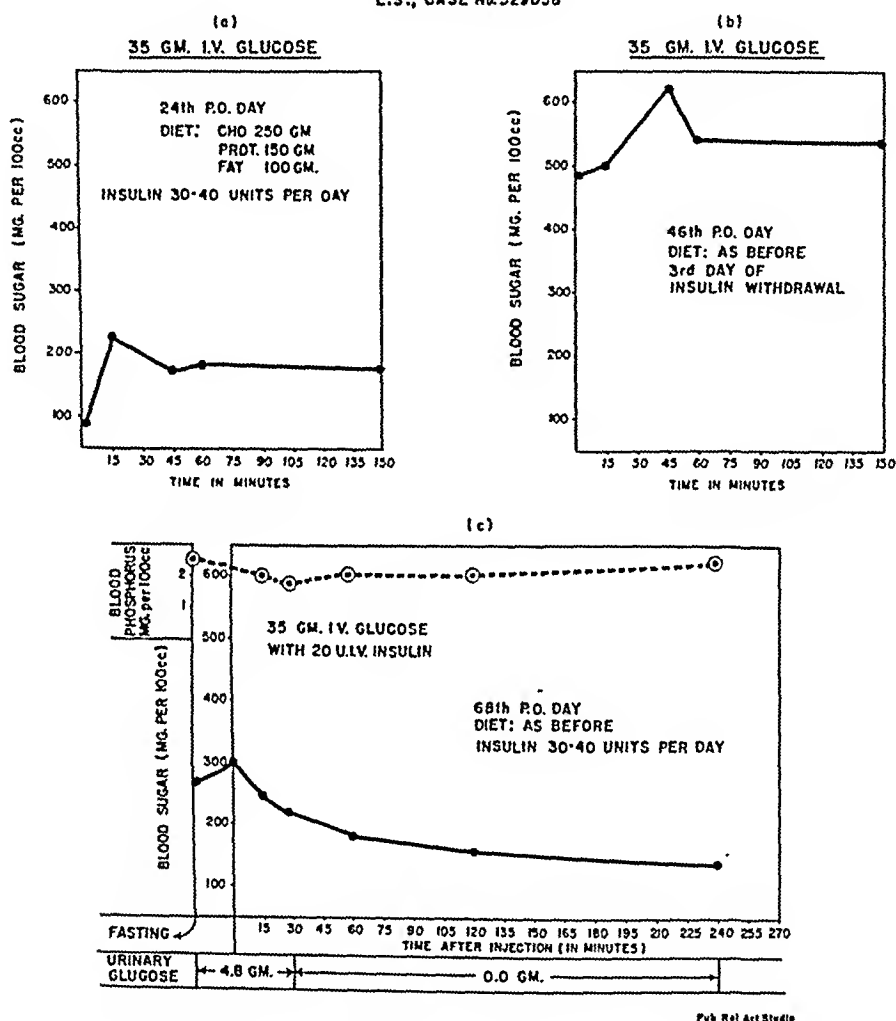


FIG. 4.—Glucose tolerance curves at various postoperative periods without [(a) and (b)] and with [(c)] simultaneous administration of insulin. (Case 3.)—(Note: The time coordinate for curve (c) is modified in order to permit the representation of an additional blood glucose determination made directly on the completion of the intravenous injection; on the abscissa this value, rather than the fasting value, is placed in the zero position.)

predictability of the blood glucose level are understandable in the terms of the physiologic activity of insulin. Figure 4 presents three characteristic sugar tolerance curves in Case 3. It can be seen from curves (a) and (b) that the glucose introduced into the blood stream is utilized at a very slow rate. Evidently there is no mechanism upon which the high blood sugar

level would exert an influence to speed up utilization by glycogenesis and oxidation. In curve (c) the presence of the insulin assures an initial utilization of the glucose, but once the insulin is expended the curve flattens out. Thus, the lack of a steady supply of insulin, gauged to the constantly changing needs of the organism seriously impairs the deposition of glycogen in the liver and its oxidation in the tissues. The periodic injection of insulin repairs this defect only in part: adequate glycogenesis and oxidation goes on only periodically, while the insulin is present. At other times, sugar may be piled up in the blood, or, because of the depleted liver glycogen, the blood sugar may be inadequate to respond to the sudden appearance of insulin in the blood stream.

The renal threshold for blood sugar may become elevated in depancreatized patients. In Case 2 blood sugar levels of 200 to 250 mg. per cent would be present without glycosuria; the threshold of this patient was variable and it seemed to be higher after periods of inadequate control. The renal threshold for glucose of Case 3 has been around 200 mg. per cent quite consistently during the past two months.

Hyperthyroidism aggravates the problem of controlling the diabetes of the patient without a pancreas. As has already been mentioned, Case 3 illustrates this point. This patient has had a basal metabolic rate varying from plus 30 to plus 59 at least for the past ten months. For the past four months her rate has been kept at around plus 30 by the administration of 150 mg. of propylthiouracil daily. Until now no effort has been made to reduce the basal metabolic rate below this level for the following reasons: Before her operation (January 31, 1948) a varying schedule of dosages with Lugol's solution and propylthiouracil was tested. She seemed to be refractory to Lugol's solution. Propylthiouracil 50 mg. t.i.d. caused a remission of her rate from plus 42 to plus 30. Since she had no other evidence of hyperthyroidism than the elevated metabolic rate (in particular, no cardiac involvement, no eye signs, no nervous system manifestations) and since she had obstructive jaundice of increasing severity, it was thought the lesser risk to operate on her rather than to wait until her metabolic rate had been further reduced. She stood the operative procedure very well and in the immediate postoperative period, upon the whole, her high metabolic rate was found to be an advantage rather than a hindrance. Since certain investigations had been started and some others planned, and since under the circumstances the high metabolic rate was causing no harm, it was decided to maintain the rate at plus 30 until the completion of the study, at the end of which an attempt will be made to lower it by increasing the dosage of propylthiouracil, or, if this should fail, by surgical means.

#### STUDIES ON INSULIN WITHDRAWAL

Several facts urged an inquiry into the behavior of the depancreatized patient after insulin withdrawal. There were observations made during the

immediate postoperative period that suggested that the depancreatized patient did not form ketone bodies as readily as one would have expected. It seemed possible that observations during a period of insulin deprivation might reveal characteristics in the course of events that might demarcate surgical diabetes from diabetes mellitus. It also seemed a practical necessity

TABLE V.—*Determinations of Blood Hemoglobin and Count, Blood Chemistry, Liver Function, Basal Metabolic Rate, Urine Chemistry, and Body Weight Before, During and After Insulin Withdrawal.*

## Case 3

Type of Determination	DAY OF OBSERVATION								
	1	2	3	4	5	6	7	8	9
BMR, % above normal	29	30	34	38	46	59	46	41	39
Respiratory Quotient	.72	.73	.70	.69	.68	.67	.66	.69	.71
Urine acetone Gm./24 hr.	0.005	0.096	0.009	0.477	1.903	3.490	0.579	0.025	
Urine $\beta$ -hydroxybutyric acid/24 hr.	0.018	0.126	0.071	0.397	3.771	7.570	0.313	0.056	
Urine sugar, Gm./24 hr.	40.2	64.3	45.3	180.0	200.0	168.7	116.5	80.0	
Urine nitrogen Gm./72 hr.		34.79			41.51			44.72	
Urine chlorides (as NaCl.) Gm./24/hr.				15.1	11.9	5.0	5.6	4.2	
Weight, lbs.	111		109	110½		108½	109½	110¼	
Hemoglobin, Gm. %	11.5	12.4	12.5			12.2	12.0	12.9	11.8
Erythrocytes, million/cu. mm.	3.76	4.09				3.60		4.20	3.57
Leucocytes, thousand/cu. mm.		11.6	13.5			14.0	17.1	11.4	13.1
Sugar (fasting) mg. %	204		136	294	313	480	156	380	297
CO <sub>2</sub> Capacity, vol. %	46	55	54	54	54	43	56	66	50
NPN, mg. %					39				
Urea N, mg. %	18.0			18.0	19.0	21.9		21.0	
Chlorides, as NaCl, mg. %	427	413	407	393	433	427	413	407	420
Sodium, mg. %	317	246	310	301	260	293	276	290	296
Potassium, mg. %	24	19	28	21		20	28	21	
Albumin/Globulin, Gm. %	3.29 3.04		2.42 4.12	3.17 2.50	3.12 2.60	3.02 2.50		3.36 2.27	3.68 1.74
Acetone, mg. %	1.9	2.0	3.3	3.7	11.7	10.8	4.7	4.0	2.4
Total Lipids, mg. %	915		865	685	714	892		756	
Cholesterol, mg. %	279		259	164	300	228	183	185	152
Cholesterol Esters, % total	53%		49%						
Icterus index, unit	15								
Bilirubin, direct, mg. %	0.13								
Bilirubin, total, mg. %	0.39								
Cephalin cholesterol	4+								
Thymol turbidity, unit	10				4+				
Thymol flocculation	Neg.				5				
Bromsulphalein % ret./hr.	12				Neg.				
Hippuric acid, oral, Gm.	2.51								
Lipase, unit	1.2			0.3			1.5		

to have some knowledge of the margin of safety that these patients possess between persistent hyperglycemia and diabetic acidosis, especially since our preference is for treatment on the hyperglycemic side. This last consideration has a special importance in view of the observation that depancreatized dogs, once they develop diabetic acidosis, are difficult to bring under control

again. For all these reasons, the following experiment was carried out in Case 3, starting on the 44th postoperative day.

After a period of adjustment of 48 hours on a diet consisting of 250 Gm. of carbohydrates, 150 Gm. of protein and 100 Gm. of fat, daily stool and urine specimens were collected for nine days (from the 46th to the 54th postoperative day). During this time the stool was quantitatively analyzed for total nitrogen, fat, fatty acids and calcium, and the urine for total nitrogen, glucose, acetone,  $\beta$ -hydroxybutyric acid and chlorides. The nine-day period of observation can be grouped in three three-day subdivisions. During the first three-day period insulin was administered in the usual amounts to maintain a satisfactory control of the diabetes. During the next three-day period insulin was discontinued. During the last three-day period insulin was again administered to re-establish diabetic control. Throughout the experiment patient was allowed to be up and around in her room. Daily determinations of numerous blood chemical constituents and of the basal metabolic rate were made; during the 4th, 5th and 6th days of observation blood sugar, blood  $\text{CO}_2$  capacity and blood acetone bodies were measured three times daily, at 7:30 A.M., 4:30 P.M. and 2:00 A.M. The results of these studies are shown in Tables V and VIII and in Figures 5 and 6.

In evaluating the significance of these findings, it must be pointed out that the control of our patient's diabetes at the beginning of the experiment was not as good as we should have liked to have it. During the preliminary period she spilled 40.2 to 64.3 Gm. of glucose and 18 to 126 mg. of  $\beta$ -hydroxybutyric acid daily. It was impossible, however, to prolong this preliminary phase since patient had come from a long distance for a strictly defined length of hospitalization and she was unwilling to change the arrangement previously agreed upon.

The clinical effects of insulin deprivation were unexpectedly innocuous. During the last 24 hours of the withdrawal of insulin the patient felt extremely weak and moderately drowsy, but otherwise was entirely comfortable. Her appetite was good during the first two days and only slightly impaired during the last day; her calculated caloric intake during the three days, respectively, were as follows: 2246, 2542 and 2334 Calories. Aside from an acetone odor of her breath she showed none of the usual clinical signs of diabetic acidosis.

Upon the whole the chemical changes likewise show a degree of acidosis that is less marked than one would expect from comparison with clinical diabetes. The daily amount of urinary acetone excreted on the last day of experiment reached the value of 3.49 Gm.; the amount of  $\beta$ -hydroxybutyric acid excreted during the same time was 7.57 Gm.\* The highest blood acetone level was 12.9 mg. per cent. In severe diabetes daily urinary acetone

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\* Expressed as acetone.

bodies have been reported in the range of 6.0 Gm. for acetone and 100.0 Gm. for  $\beta$ -hydroxybutyric acid.<sup>15</sup> Thus, the degree of acidosis of this patient after three days of complete deprivation of insulin could be classified as moderately severe in terms of clinical diabetes. The significance of this

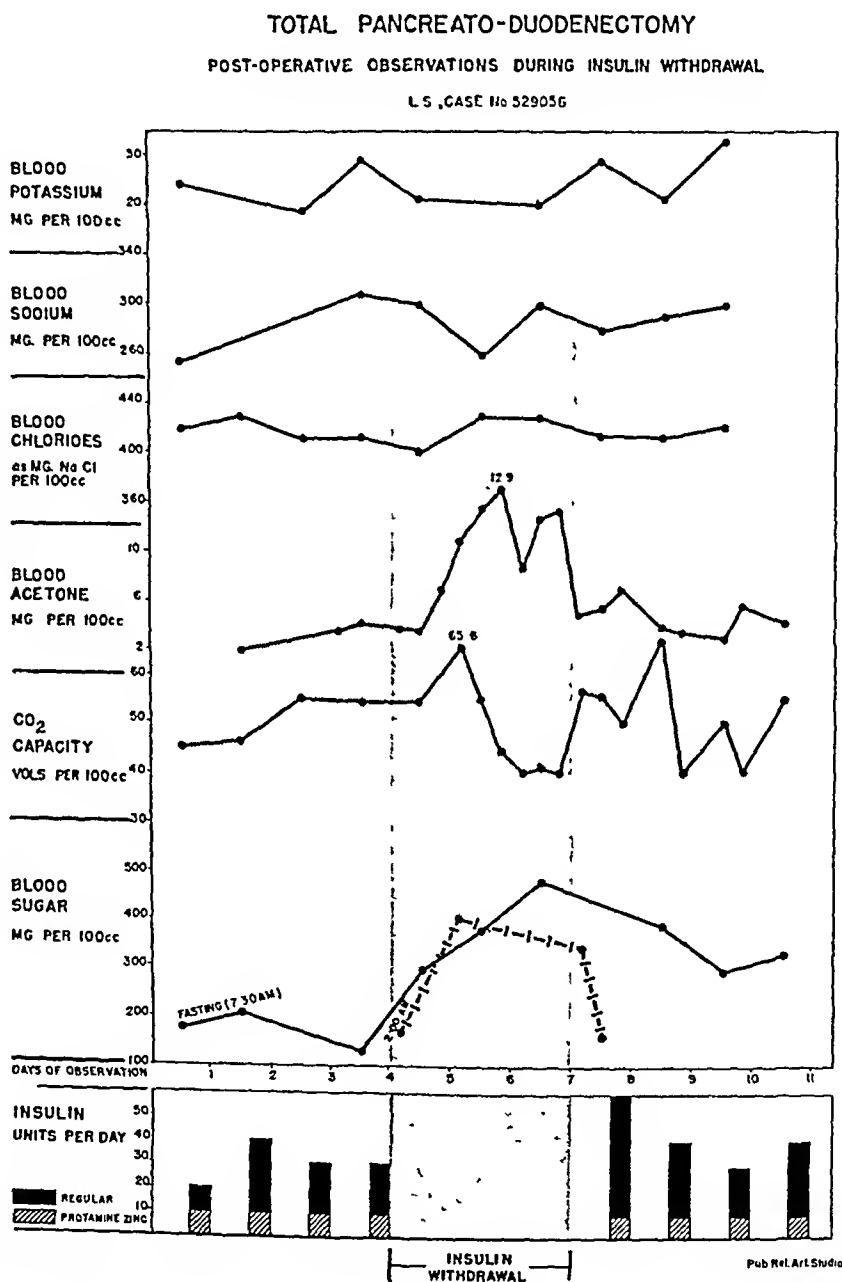


FIG. 5.—Blood postassium, sodium, chlorides, acetone, CO<sub>2</sub> capacity and sugar levels before, during and after insulin withdrawal; daily insulin requirement. (Unless otherwise marked, values are fasting.) (Case 3.)

fact is probably enhanced by the presence of a high metabolic rate in the patient.

The basal metabolic rate during the period of ketosis rose from an initial plus 34 to plus 59. The respiratory quotient declined from .73 to .66. The patient lost two pounds of weight during the experiment.

The levels of blood potassium and sodium showed no significant change. The other chemical constituents of the blood likewise remained within normal limits. The temporary increase in the urinary chloride excretion very likely was the result of diuresis.

The relative mildness of the acidosis was further attested by its relatively swift disappearance on treatment. At the completion of 72 hours of insulin deprivation a urethral catheter was inserted and urine from the bladder was tested every two hours. For Benedict reactions over 2 plus, 20 units of

TABLE VI.—*Preoperative Nitrogen Balance*

## Case 3

Calculated diet: Carbohydrate 300 Gm., protein 90 Gm., fat 93 Gm.

Medication: none

Period of Study Days	Urine N Gm.	Stool N Gm.	Total Output N Gm.	Total Intake N Gm.	N Balance Gm.
6	49.81	38.78	88.59	86.16	-2.43

Daily averages: urinary N, 6.46 Gm.; fecal N, 6.30 Gm.

regular insulin were administered hypodermically as an initial dose and 10 units thereafter. No other treatment was given. After the injection of 60 units of insulin in the course of ten hours, the Benedict reaction showed only a trace of glucose, and there was only a trace of acetone in the urine. The fasting blood sugar at this time was 151 mg. per cent. The patient continued to have a moderate glycosuria for the subsequent 48 hours of observation, but the blood and urinary acetone remained near normal levels.

Six hours after the beginning of the resumption of insulin the patient's drowsiness had cleared. She gradually became more active and in 24 hours she was going about her business as usual. She insisted on leaving the hospital on schedule, 72 hours after the termination of the period of insulin withdrawal. (For this reason her diabetic control could not be completely re-established.)

Concurrently with the investigation of the effects of insulin withdrawal, nitrogen balance studies were carried out. The patient was offered a diet calculated to consist of 250 Gm. of carbohydrates, 150 Gm. of protein and 100 Gm. of fat. She took the diet well, her intake varying from 2246 to 2672 Cals. during the nine days. Collection of the specimens was for three-day intervals. The nitrogen content of the actual intake was determined by analysis. The carbohydrate and fat contents of the ingested food were not measured analytically. The patient continued to be given her previous medications (pancreatin (U.S.P.) 4.0 Gm., choline chloride 4.0 Gm., propylthiouracil 0.150 Gm. daily).

Table VIII shows the results of this study. The significant change noted was the increase in both the daily urinary and the daily fecal nitrogen excretion. Whereas during a previous nitrogen balance study, during which

TOTAL PANCREATO-DUODENECTOMY  
URINARY EXCRETION OF GLUCOSE,  $\beta$ -HYDROXYBUTYRIC ACID AND CHLORIDES  
DURING INSULIN WITHDRAWAL  
L.S. CASE No. 529056

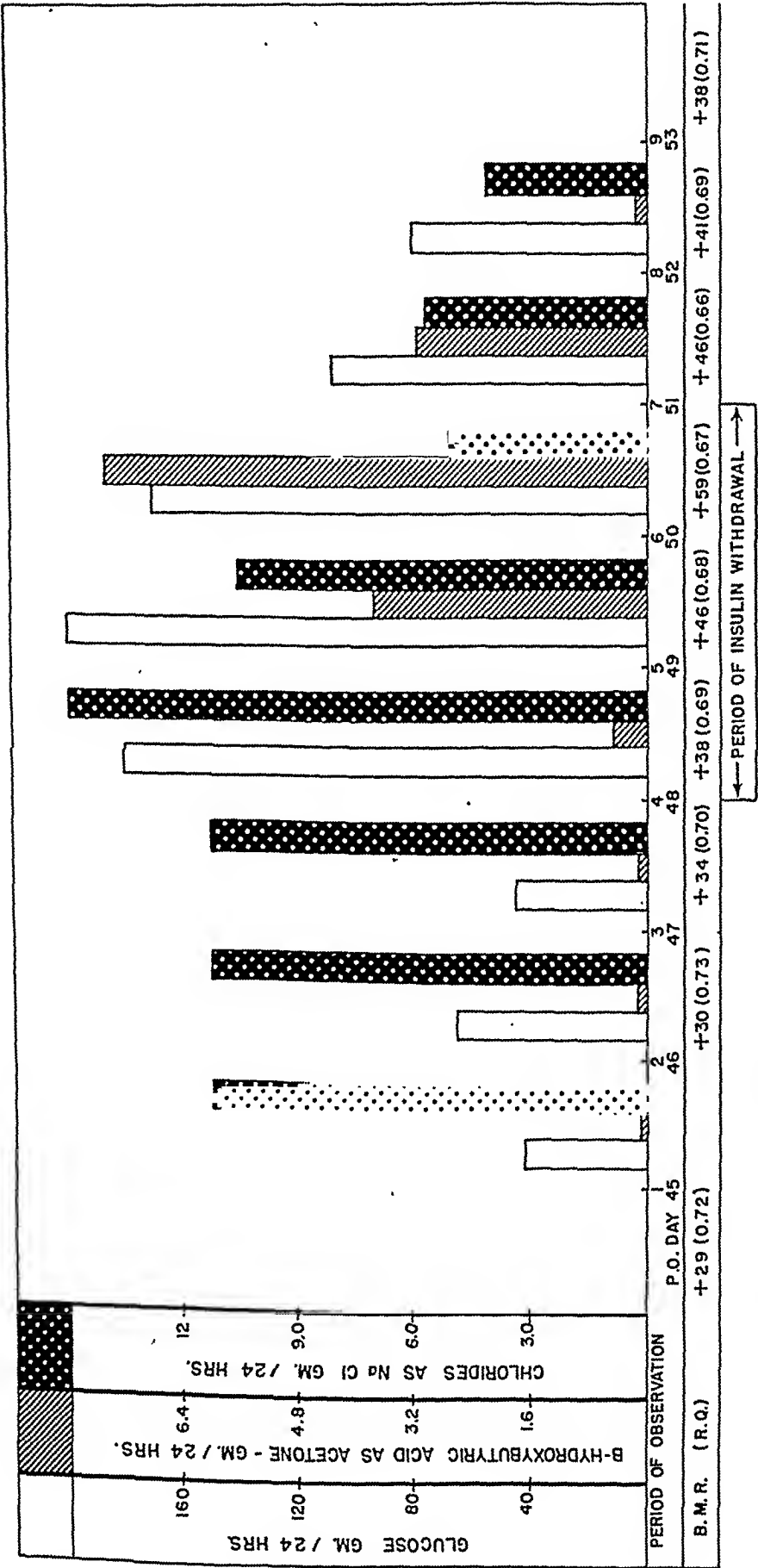


Fig. 6.—Urinary excretion of glucose,  $\beta$ -hydroxybutyric acid and chlorides during insulin withdrawal. Changes in the basal metabolic rate and in the respiratory quotient. (Case 3.)



patient received the same medications including pancreatin, the daily average urinary nitrogen was 6.79 Gm. and the daily average fecal nitrogen was 2.21 Gm. (Table VII), these values rose to 13.44 Gm. and 4.38 Gm., respectively, during the period that includes the three days of insulin withdrawal as well as the three days preceding it and the three days following it. There was an average daily nitrogen deficit of 5.77 Gm. Unfortunately, the intake of nitrogen was not determined daily, but was for the total period of nine days. Thus, it is not possible to tell precisely the magnitude of nitrogen deficit for the three days of insulin deprivation as compared to the other two periods. Since, however, the fecal nitrogen loss was very

TABLE VII.—*Postoperative Nitrogen Balance.*

## Case 3

*Calculated diet:* Carbohydrate 250 Gm., protein 150 Gm., fat 100 Gm.,

*Medication:* Pancreatin (U.S.P.) 4.0 Gm./day.

Period of Study * Days	Urine N Gm.	Stool N Gm.	Total Output N Gm.	Total Intake N Gm.	N Balance
5	33.96	11.04	45.00	69.21	24.21

*Daily averages:* Urinary N, 6.79 Gm.; fecal N, 2.21 Gm.

\* Nineteenth to twenty-third postoperative days.

constant from period to period, it is possible to refer to the urinary nitrogen as an index of the deficit per period. The urinary nitrogen in the three periods was 34.79, 41.51 and 44.72 Gm., respectively. Thus the urinary nitrogen loss in the second period was 19.3 per cent and in the third period 28.5 per cent above that in the first period. The increase in the loss of urinary nitrogen may probably be ascribed to the effects of ketosis, largely resulting from the stepped up protein catabolism. The diuresis (up to 4500 cc. a day) during the second and third periods was very likely another factor. It is not easy to explain the increase in fecal nitrogen. One might suppose that the pancreatin dosage, which was small but had previously proved adequate, apparently became insufficient during the altered metabolic demands of the period of observation. Strangely, however, the efficiency of fat digestion showed no important deterioration during this time (Table IX).

No significant change was found in the urinary and fecal calcium excretion during the same period of observation.

#### THE EFFECTS OF THE ABSENCE OF EXTERNAL PANCREATIC SECRETIONS SUBSTITUTION THERAPY

*Observations on Fecal Nitrogen and Fat.*—Studies of fat and protein digestion were made in Case 3. A few scattered observations of some interest were gathered in Cases 1 and 2.

In case 1 there was no quantitative determination of the stool fat and nitrogen content before operation. On the eighth postoperative day, patient

TABLE VIII.—Postoperative Nitrogen and Calcium Balance Partly During Insulin Withdrawal  
 Case 3

Calculated Diet: Carbohydrate 250 Gm., protein, 150 Gm., fat 100 Gm. — Medication: Pancreatin (U.S.P.) 4.0 Gm./day.									
Period of Study (P. O. Day)	Urine N Gm.	Stool N Gm.	Total N Output Gm.	Total N Intake Gm.	N Balance Gm.	Urine Ca Gm.	Stool Ca Gm.	Total Ca Output Gm.	Total Ca Intake Gm. Ca Balance Gm.
46th-48th	34.79	13.75	48.54			1.084	3.109	4.193	
49th-51st*	41.51	13.14	54.65			1.346	1.216	2.562	
52nd-54th	44.72	12.55	57.27			0.994	4.651	5.645	
			160.46	108.52	-51.94			12.400	-0.322
Daily average values: Urinary N, 13.44 Gm.; fecal N, 4.38 Gm.; N deficit, 5.77 Gm. — Urinary Ca, 0.380 Gm.; fecal Ca, 0.997 Gm.; Ca deficit, 0.036 Gm.									
*Insulin withdrawn on the 49th to 51st postoperative days.									

was placed on pancreatin (U.S.P.) in the dosage of 3.0 Gm. daily. He complained of gastric distress following the ingestion of this drug and often omitted it. During the third postoperative month he had completely stopped taking the medication. On a prescribed diet of carbohydrates 200 Gm., protein 120 Gm. and fat 60 Gm., on the 100th and 101st postoperative days the average daily fecal nitrogen was 0.8 Gm. and the amount of total fats in the stool was 38.7 per cent of the dry weight (normal average being 17.5 per cent<sup>16; 17</sup>). Patient had no serious disturbance of bowel movements. During the 10th postoperative month, after several days of regular pancreatin intake in the dosage mentioned, and on a diet of carbohydrate 300 Gm., protein 135 Gm., fat 100 Gm., on three alternate days the percentage by dry weight of the total stool fat was as follows: 25.6, 15.3 and 21.9.

Preoperative quantitative data on the stool fat and nitrogen are lacking also in Case 2. On the 20th, 21st and 22nd postoperative days the stool was collected and analyzed quantitatively for nitrogen and fat; the nitrogen content of the urine excreted during this time was also determined; the prescribed diet contained 250 Gm. of carbohydrate, 120 Gm. of protein, and 70 Gm. of fat. At this time patient was receiving 75 Gm. of pancreatin (U.S.P.) daily. The amount of total fat in the stool on the three days was 28, 19 and 22.4 per cent of dry weight respectively; the average daily fecal nitrogen was 0.93 Gm. and the daily urinary nitrogen 6.05 Gm.

The meaning of such random data is doubtful. The nitrogen determinations on the stool and urine without a knowledge of the true intake and after such short collections must be disregarded. Some remarks should be made, however, in connection with the values for stool fat. In Case 1 it is surprising to find a stool fat content very near the normal range on an ingestion of pancreatin as low as the

equivalent of 3.0 Gm. of U.S.P. pancreatin. It is also noteworthy that the same patient had no serious diarrhea when his stool contained 38.7 per cent of fat by dry weight. The very large doses of pancreatin was prescribed in Case 2 in an attempt to control patient's annoying frequency of bowel movements, the rather hasty assumption having been made that this was due to incomplete digestion of the dietary fat. Quantitative analysis of the stool disclosed that total fats were in the upper range of normal values. Eventually the dosage of pancreatin was reduced and the diarrhea controlled by conventional means of treatment. This observation, namely that frequent loose stools after total pancreatectomy may be due to causes unrelated to the absence of pancreatic enzymes, was made also in Case 3.

TABLE IX.—*Postoperative Fat Content of Stool*

## Case 3

*Calculated Diet:* Carbohydrate 250 Gm.; protein 150 Gm.; fat 100 Gm.—*Medication:* Pancreatin (U.S.P.) 4.0 Gm./day

P.O. Day	Wet Wt. of Stool Gm.	Wt. of Stool Fat Gm.	Fat Gm. per 100 Gm. Dry Stool	Wt. of Fatty Acids Gm.	Fatty Acids Gm. per 100 Gm. Fat
46	380	39.4	34.8	31.9	81
47	521	43.7	30.5	35.9	82
48	196	19.2	32.6	15.7	81
50	472	14.0	11.6	9.5	67
52	504	15.7	12.2	10.0	64
53	284	11.5	12.5	7.6	66
54	349	15.0	13.5	9.4	63

*Average daily fecal fat:* 22.6 Gm. (21 per cent of dry wt.)

*Average daily fecal fatty acids:* 17.1 Gm. (75.7 per cent of fat)

*Remark:* Average *preoperative* fat content of stool on a diet containing about 90 Gm. of fat, and without medication (48 hr. collection): 52.3 per cent of dry wt. of feces.

(In neither case, however, did the stool have the characteristics of steatorrhea.)

It should be pointed out that the pancreatin preparations used in the above cases, as well as in the studies to be described, were not uniform. All dosages are expressed in terms of U. S. P. pancreatin, the claims of potency by the manufacturer being used as basis for transcribing the values.

More systematic investigations regarding protein and fat digestion and absorption were carried out in Case 3.

Ten days before the date of operation, a six-day nitrogen balance study was begun. In this as in the following studies the collections of stool and urine as well as the samples and refused portions of the diet were pooled for three-day (rarely, two-day) periods. The beginning and end of each period was designated by charcoal and carmine markers. The calculated diet contained 300 Gm. of carbohydrate, 90 Gm. of protein and 93 Gm. of fat daily. No medication was given. The results of this study are shown in Table VI. The average daily fecal nitrogen was high, representing 39.4 per cent of the daily nitrogen intake. As shown by enzyme studies of the duodenal contents this patient had a complete obstruction of the main pancreatic duct preoperatively. The insufficiency of protein digestion

was, therefore, to be expected. Determination of the fat content of the stool after a 48 hour collection, 14 days before operation showed a total fat value of 52.3 per cent of dry weight on a diet containing about 90 Gm. of fat. Thus, the fat digestion was similarly impaired. (As will be recalled, one of patient's important preoperative complaints was a severe persistent diarrhea consisting of bulky, soft or liquid stools.)

Patient began taking food by mouth on the fourth postoperative day. After a trial with several brands and dosage schemes of pancreatin, the preparation "panteric granules" (Parke, Davis and Co.) was selected in a dosage equivalent to 4.0 Gm. of U. S. P. pancreatin daily. This amount was selected empirically. It was well tolerated and although it appeared very small, during its early administration patient's stools were of normal appearance and size.

On the 19th to 23rd postoperative days a five-day nitrogen balance study was undertaken in order to ascertain whether the dosage of pancreatin administered was in fact adequate. The data obtained are listed in Table VII. It is evident that patient was in positive nitrogen balance and that the daily stool nitrogen was not above the normal average. Patient was discharged on the same diet and same dosage of pancreatin on the 25th postoperative day.

She was readmitted on the 44th postoperative day for further investigations. In conjunction with studies on carbohydrate metabolism, nitrogen balance studies were also carried out. The results and the significance of the data so obtained have already been dealt with. Some further comment may be made on the study of the loss of fecal fat during this period, referred to in the same paragraph (Table IX). This was not a true balance study since the intake of fat was not quantitatively determined. The trend of the findings is definite enough and the number of determinations sufficiently large, however, to permit the conclusion that fat digestion at this time was essentially normal. The behavior of fecal calcium, showing no excessive loss, would also confirm this. The high percentage of fatty acids in the lipid mixture may be interpreted as another evidence of efficient fat-splitting in the intestinal tract. (However, the significance of the neutral fat/fatty acid ratio has been questioned.) Nevertheless, in order to avoid any possibility of underdosage at the end of the experiment the amount of pancreatin given was raised to 8.0 Gms. daily (2.0 Gm. with each one of four meals); patient was dismissed on this dosage, with her diet as before.

On this regimen and medication she gained eight pounds in four weeks after her return home; she has remained free from diarrhea, and has been in excellent general health.

Our studies have not determined the optimum dosage of substitution therapy for the total lack of pancreatic enzymes. They suggest, however, that the large doses of pancreatin that are at times recommended<sup>18</sup> are prob-

ably unnecessary. They further seem to show that the appearance of diarrhea in the absence of pancreatic enzymes is dependent on the amount of undigested fat rather than on the loss of nitrogenous substances in the stool. Moreover, an increased loss of nitrogen in the stool may seemingly take place in the presence of relatively normal fat digestion.

#### POSTOPERATIVE AMYLASE AND LIPASE CONTENT OF BLOOD

It was an interesting finding that, as judged by the conventional methods of determination, lipase and amylase do not completely disappear from the blood stream for many weeks after total pancreatectomy. Amylase

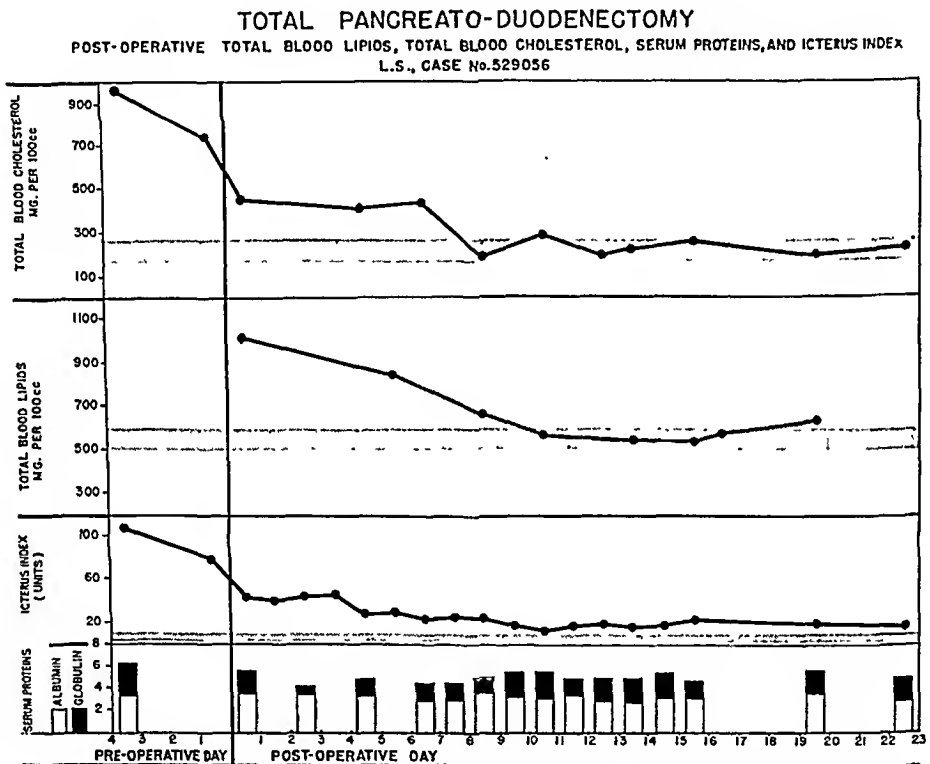


FIG. 7.—Changes in blood lipids and icterus index in a case of normal postoperative recovery. (Case 3.)

was detectable forty weeks postoperatively in case 1 (Table II). Examination in the 13th postoperative week revealed the presence of blood lipase in Case 3.

#### LIPID METABOLISM

##### THE QUESTION OF LIPOTROPIC FACTOR

In order to prevent changes in the liver that, on the analogy of animal experiments,<sup>19</sup> were expected to take place in the depancreatized human, the administration of choline chloride was begun soon after operation in daily doses of 3 to 4 Gms. in Cases 2 and 3. Case 1 received no choline chloride or other lipotropic substance. For the last month of observation the drug

was also discontinued in Case 3. When the liver was examined at autopsy in Case 1 after 14 months of survival, it was found to show no evidence of parenchymal change. Liver function tests before death likewise failed to show impairment (Table II). In Case 3 liver function tests, in particular the bromosulphophthalein test, revealed no deterioration during the short period of deprivation of choline (Table IV).

Both these patients received pancreatin daily (Case 1 only intermittently), and pancreatin contains choline. The daily preventive dose of choline, however, is calculated as 4-5 Gm., and the choline content of the pancreatin used was only 8.28 mg./Gm.<sup>20</sup> Thus pancreatin could not have served as a source of the allegedly needed choline.

From the findings in the two cases mentioned it appears that a lipotropic pancreatic substance either is unnecessary for lipid metabolism in the human, or, if it is required, it is supplied in the average diet in sufficient quantity. It seems superfluous to provide the lipotropic factor in the form of medication.

With reference to lipid metabolism in the depancreatized patient, the *trends in blood lipid levels* may also be briefly mentioned. Unfortunately the amount of total blood lipids was not preoperatively determined in any of the cases. In *Case 1* postoperative total lipids and cholesterol were measured rather frequently. (Table II shows some of the values.) During the first three postoperative weeks the amount of total lipids ranged between a low of 563 mg. per cent and a high of 709 mg. per cent; no cholesterol determinations were made during this time. During the fifteenth postoperative week the ranges of total blood fats and total cholesterol were as follows: lipids, 528-525 mg. per cent, total cholesterol, 107-128 mg. per cent; during the fortieth postoperative week the total lipids were 390 mg. There were no further determinations. In *Case 2* we have only the following values: Preoperative total cholesterol, 276 mg. per cent; eighth postoperative week, total lipids, 390 mg. per cent; twelfth postoperative week, total lipids, 420 mg. per cent. In *Case 3* the levels were as follows: preoperative total cholesterol 980 and 946 mg. per cent (10 per cent being ester); during the first three postoperative weeks the total cholesterol steadily decreased from 450 to 200 mg. per cent; the esters rose from 10 per cent to 40 per cent of the total cholesterol;—there was no preoperative total lipid determination made; on the first postoperative day the total blood lipids were 1020 mg. per cent and during the first three weeks after operation they dropped to 613 mg. per cent; in the seventh postoperative week, total cholesterol was 235-279 mg. per cent (esters 43-53 per cent); total lipids, 694-915 mg. per cent. The values for the period of study with insulin withdrawal are listed in Table V. The blood levels during the thirteenth week were: cholesterol 210 mg. per cent (esters 43 per cent), total lipids 593 mg. per cent (last determinations).

These data are not complete enough to allow definite conclusions. They do show, however, some suggestive trends in Cases 1 and 2. In case 1 observations over the space of 40 weeks reveal a fairly consistent decline in the total lipids, and to a less extent in the total cholesterol. The very few determinations in case 2 would seem to follow the same direction. No such trend is noted in case 3; the cholesterol and total fat values did decline in the immediate postoperative period, but this change was merely a return from a very high preoperative level to a more nearly normal range (Fig. 7). There was a definite increase in the lipids during the

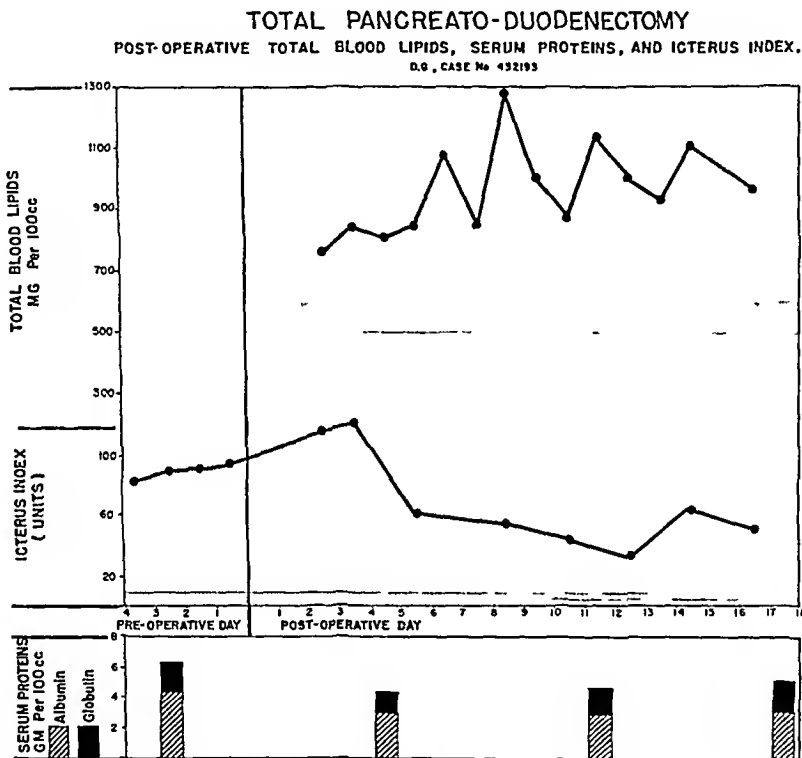


FIG. 8.—Changes in blood lipids and icterus index in a fatal case.

interval of insulin withdrawal and the presence of ketosis, but the most recent determinations were again normal.

Another observation on lipid metabolism should perhaps be recorded although it was made in a case not included in the present study. This patient died 18 days after total pancreatoduodenectomy for carcinoma of the pancreas. The cause of death, verified by autopsy, was hepatic insufficiency due to very advanced fatty degeneration of the liver. The patient's blood lipids became markedly elevated postoperatively and remained high until death (Fig. 8). In the same patient the icterus index also failed to return to normal although there was no mechanical obstruction to the flow of bile from the common duct into the jejunum. Identical observations on the behavior of the icterus index in at least two more cases of total pancreatec-

tomy have made us regard the icterus index as a good measure of the functional state of the liver in the immediate postoperative period; in the presence of a functioning choledochal stoma a rising index after the first three postoperative days suggests a failing liver. Whereas, in the case described above the hepatic failure was associated with fatty parenchymatous degeneration of the organ, in one of the other two cases such an association was not present, and in the third case autopsy was not done, and thus no conclusive evidence of the presence or absence of such changes could be had. Nor can we be certain that the fatty degeneration of the liver in the case in question was etiologically linked with the interruption of the normal physiological function of the pancreas by the operation.

#### SUMMARY

After the presentation of short resumé's of the clinical histories of three cases of total pancreatoduodenectomy, two of whom survived the operation for three and 14 months respectively, and one of whom is living and well four months after operation, observations are described on the early and late changes in the carbohydrate metabolism, on the alterations in the fat and protein digestion and absorption, and on the trends and significance of the blood levels of pancreatic enzymes, lipids and bilirubin in the depancreatized patient. The effects of the withdrawal for 72 hours of insulin in such a patient are reported.

#### CONCLUSIONS

(1). In the experience of the authors, the characteristics of the diabetes in patients after total pancreatectomy are (a) a relatively low insulin requirement (20-60 daily units); (b) a sensitivity to insulin, and (c) frequent and often unpredictable fluctuations in the blood sugar level.

(2). Because of these characteristics, the safe way of controlling the diabetes is to maintain the fasting blood glucose level on the hyperglycemic side (150 + mg. per cent).

(3). The ketosis that developed in a depancreatized patient after a 72-hour period of deprivation of insulin was comparable to a moderately severe ketosis in diabetes mellitus.

(4). An elevated basal metabolic rate renders the control of total surgical diabetes more difficult.

(5). There are suggestive evidences that the pathophysiology of total surgical diabetes is not identical with diabetes mellitus as understood in terms of the conventional clinical type.

(6). The means available to correct the consequences of the absence of the external pancreatic secretion are effective. The dosage of pancreatin recommended in the past for substitution therapy is probably high. Six to 8.0 Gm. of pancreatin (U.S.P.) daily in the cases observed was sufficient to



assure satisfactory fat digestion, and to maintain a normal state of nutrition and, in one instance, a positive nitrogen balance.

(7). Lipase and amylase are demonstrable in the blood stream for long periods of time after total pancreatectomy.

(8). No evidence of a deficiency of the lipotropic pancreatic factor was noted on a maintenance diet of high protein and average carbohydrate and fat content.

(9). No characteristic trends were observed in the changes of blood lipid values.

NOTE: The authors are greatly indebted to Dr. Oliver H. Gacbler, for his valuable and generous help with many of the problems of this study.

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DISCUSSION.—DR. LAURENCE S. FALLIS, Detroit (closing): I have only one or two observations of practical importance to make. First, I should like to comment on the value of pancreatic enzyme studies preoperatively. We have found that the absence or marked reduction of pancreatic enzymes in the duodenal drainage, as described by Whipple and his associates, in conjunction with evidence of obstructive jaundice is strongly suggestive of carcinoma at the head of the pancreas. In six of eight cases recently observed, the impression gained was of help in establishing the differential diagnosis. There is also no doubt that the control of diabetes in these patients on the hyperglycemic side is by far the safer procedure. The objection may be raised that a long-continued hyperglycemic state hastens the degenerative changes so often observed in chronic diabetes, but of course none of these patients has survived over a sufficient period to prove or disprove that point. I should like to mention also that in the control of surgical diabetes the use of protamine zinc insulin has been of considerable advantage. Its long-lasting action more nearly approaches the even flow of the secretory mechanism of island tissue. But it still lacks the moment-to-moment adjustment that is so often necessary, and we have observed that even with protamine zinc insulin, control is difficult because of the unusually high insulin sensitivity.

# COLORIMETRIC DETERMINATION OF AMYLASE<sup>°†</sup>

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A SIMPLE COLORIMETRIC method for the determination of amylase was devised because of the great importance of assays of this enzyme in clinical medicine and physiology. The significance of amylase in surgery has been abundantly demonstrated. Curiously, the conditions governing the determination of the activity of amylase have not been studied systematically, so that previous amylase methods have necessarily been more or less empirical and haphazard. The kinetics of this enzyme were examined critically by us and the results are included in this paper.

All methods for determining amylase have rested on one of three principles, the iodometric, saccharogenic or viscosimetric.

The iodometric principle was first advanced in quantitative form by Wohlgemuth in 1908.<sup>1</sup> Amylase activity was expressed in terms of the time required for a given enzyme sample to render a starch substrate colorless to iodine. Many modifications, based on this principle, have been used<sup>2, 3</sup> in an effort to reduce the subjective factor in color estimation. Since an excess of substrate must be present for optimal enzyme activity, an end-point which calls for total disappearance of the substrate is completely unsatisfactory. Most of the adaptations of this principle have, therefore, sought an end-point short of complete decolorization such as the point where the red color due to erythroextrins takes the place of the blue of starch.<sup>4</sup> Redfern<sup>5</sup> introduced a glass color standard for comparison with starch-iodine colors before the achromic point is reached, but the technic is crude. The error of subjective color estimation has been the most important limitation of the iodometric principle.

The saccharogenic principle, now widely used,<sup>4, 6, 7, 8</sup> is based on measurement of the reducing groups produced by the hydrolysis of starch. Thus, by measuring the reducing power of the enzyme-substrate mixture before and after incubation one obtains a measure of enzyme activity. Reduction is measured by a copper method such as that of Shaffer and Somogyi<sup>9</sup> and results are expressed in terms of milligrams of glucose liberated. The accuracy of these methods is limited to materials in which initial reducing power is low. High blanks necessarily occur in diabetic urine and blood. Moreover, the preparation of the substrate in the valuable method of Somogyi<sup>4</sup> is inconvenient.

The viscosimetric principle, described by Davison,<sup>10</sup> depends upon the decrease in viscosity of the starch substrate as the average molecular size is

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† Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

reduced by hydrolysis. Viscosity measurements are made in an Ostwald viscosimeter, the time required to reduce the viscosity by 20 per cent being taken as an expression of enzyme activity.<sup>11</sup> Elman and McCaughan<sup>11</sup> recommend this principle as the only means of measuring the full range of hydrolysis rather than the disappearance of substrate or the production of end products alone. The following sources of error are inherent in this method: the time of incubation is necessarily variable since viscosity change does not bear a linear relation to time; there is an initial change in viscosity which occurs with addition of the enzyme sample; further, the viscosity of the enzyme does not change during incubation.<sup>12</sup> Comparisons of the available methods have been made by several authors.<sup>6, 12-16</sup>

#### THEORY OF THE METHOD

Colorimetric methods are well suited to use in quantitative enzyme assays. If either the substrate or one of the reaction products is colored it may be measured directly in the photoelectric colorimeter. Also, reagents may be added to produce color with the substrate or a reaction product.

The blue color of the starch-iodine complex affords an opportunity to apply the second of these colorimetric procedures. Its depth with an excess of iodine was found by us to be strictly proportional to the amount of starch present.

A plot of the logarithm of the colorimeter reading against the arithmetic concentration of starch in the presence of a constant amount of iodine gives a straight line. By using this curve as a reference standard one may readily determine the amount of starch present in an unknown sample to within 0.02 mg.

Up to 4 mg. of starch with 4 ml. of 0.01 *N* iodine reagent will give colors which when diluted to 100 ml. can be conveniently read in the Evelyn photoelectric colorimeter, an instrument used in all of our work. A 660 millimicron filter eliminates all extraneous color such as that due to the excess iodine and to the dextrans formed in amylolytic hydrolysis. In this range a 100 per cent change in iodine concentration has only a slight effect on the color. In this way, measurement of the color given with iodine by aliquot samples of the starch-enzyme mixture before and after incubation permits enzyme activity to be expressed in terms of milligrams of substrate hydrolyzed.

*Starches.* The source and method of preparation of the starch influence its solubility, the stability of solutions, the initial reducing power, and the viscosity, as well as susceptibility to enzymatic hydrolysis.

We have found that high-grade potato starches are very soluble and uniform. Clear solutions give more intense colors with iodine per weight than any other starch examined and are of low viscosity, suggesting that this starch is composed of comparatively long, unbranched molecules. A soluble starch was, therefore, used throughout.

*The Starch-Iodine Color.* At neutrality the starch-iodine color is stable for many hours both in the dark and the light. We have confirmed the

finding of Swanson<sup>17</sup> that it gives a single peak absorption curve in the Beckman spectrophotometer having its maximum at 590 mu. The color disappears at alkaline pH values probably because the iodine is displaced from the starch molecule by hydroxyl ions. Dialysis of the complex removes the iodine completely in a few minutes, color being restored on addition of more iodine which is evidence that the bond between starch and iodine is a loose one.

#### KINETICS OF STARCH HYDROLYSIS BY AMYLASE

The kinetics of starch hydrolysis by amylase were investigated in order to outline proper conditions for an assay procedure. Fresh human urine was the source of enzyme.

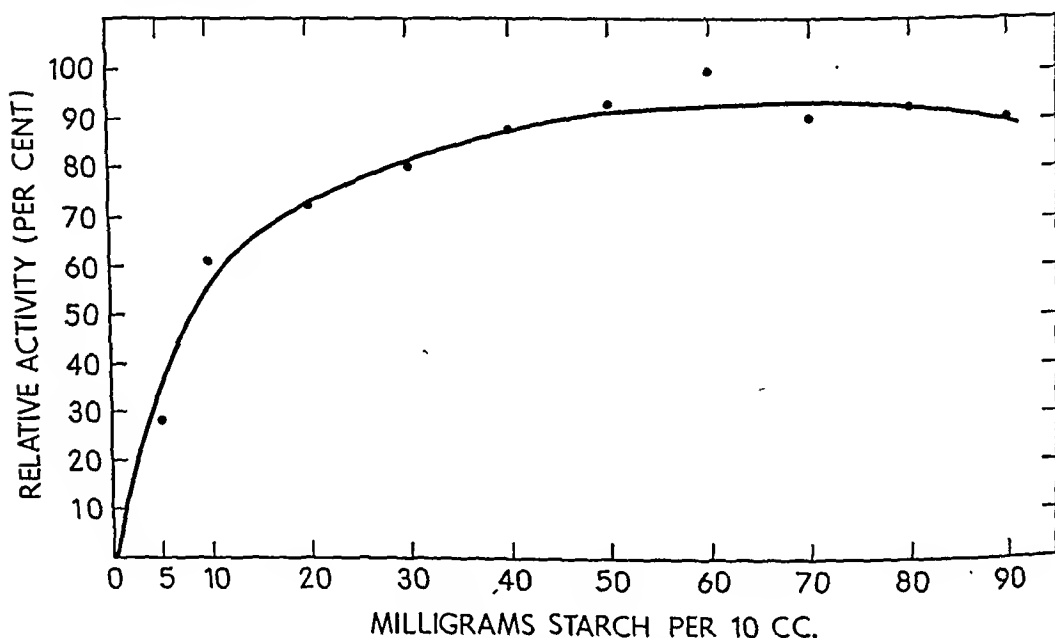


FIG. 1.—The effect of substrate concentration on the rate of enzymatic hydrolysis of starch. Progressive amounts of starch were incubated for one hour with a constant amount of enzyme and phosphate buffer at pH 7 and 37° C.

*Effect of Substrate Concentration.* A plot of substrate concentration against reaction velocity yields a typical curve (Fig. 1) showing that maximum velocity, or saturation of the enzyme with substrate, was reached at about 45 mg. per 10 ml. We therefore chose a substrate concentration of 80 mg. per 10 ml. for all subsequent work. In this range change in substrate concentration has a minimal effect on the velocity.

A quantitative expression of enzyme-substrate affinity which helps to characterize enzyme systems is afforded by the Michaelis and Menten constant,<sup>18</sup> most accurately found by plots of the reaction velocity with varying substrate concentrations according to the method of Lineweaver and Burk<sup>19</sup> (Fig. 2). Values for starch cannot be expressed in terms of molecular weight and so have been expressed in terms of milligrams per 10 ml. The

Michaelis and Menten constant for the starch employed by us, using a single enzyme concentration, was 7.14 mg. per 10 ml. This agrees well with the value of 7.9 mg. per 10 ml. found by Hanes<sup>20</sup> who used a saccharogenic method.

*Effect of Enzyme Concentration.* A linear relation between enzyme concentration and rate of hydrolysis is the most important prerequisite of any enzyme assay. Although the change in starch-iodine color is theoretically produced by only the initial steps in starch hydrolysis, this linear relation (Fig. 3) proves it to be an adequate measure of enzyme concentration.

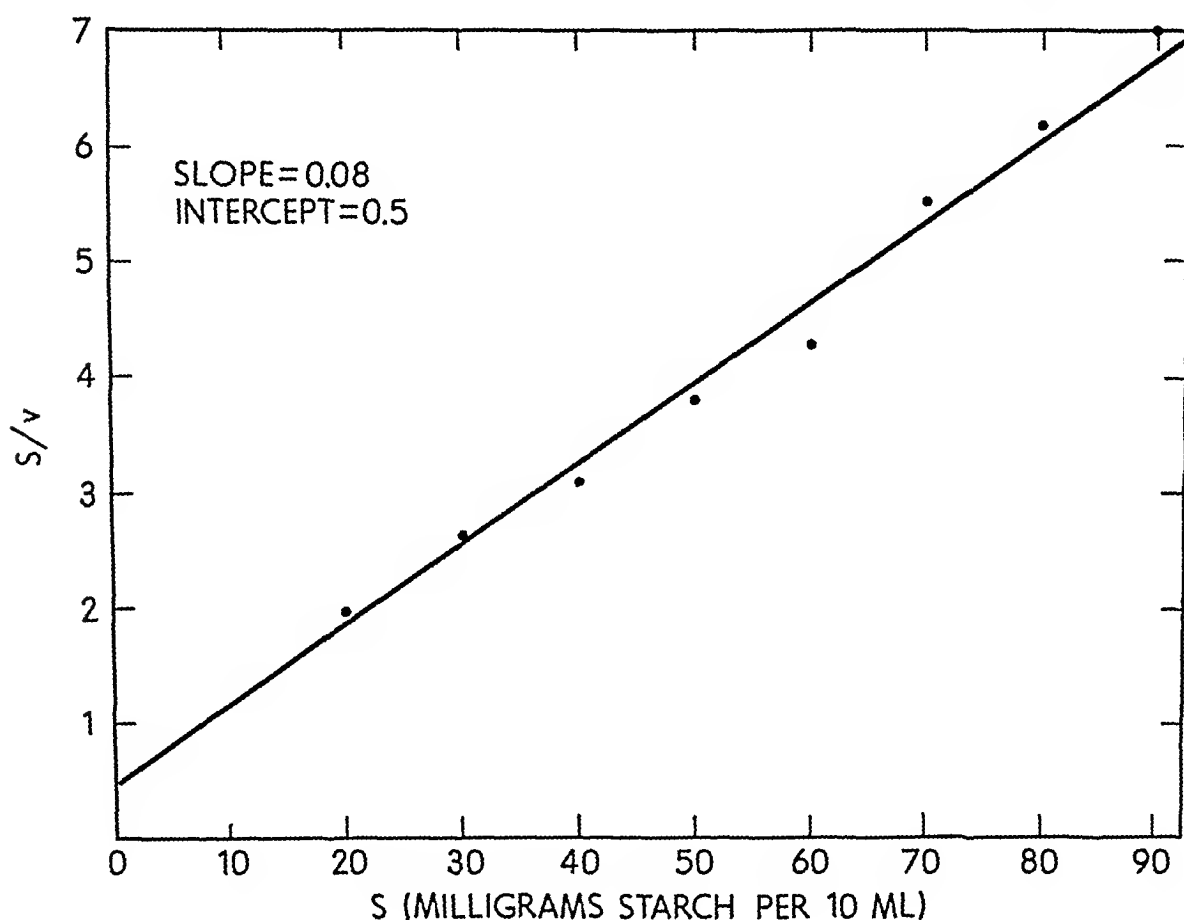


FIG. 2.—Data from Fig. 1 plotted according to Lineweaver and Burk. Substrate concentration,  $S$ , in mg. per 10 ml., is plotted against  $S$  divided by the velocity of hydrolysis,  $v$ , expressed as milligram of starch hydrolyzed per hour. From the intercept and slope of this curve the Michaelis and Menten constant was calculated to be 7.14 mg./ml.

*Effect of Time.* The time course of hydrolysis (Fig. 4) is linear, equal amounts of starch being hydrolyzed in equal times until the enzyme is no longer saturated with respect to substrate. The prediction from Figure 3 that the limit of saturation will be reached when about 35 mg. of the 80 mg. of starch is hydrolyzed is confirmed experimentally by the sharp decrease in velocity at this point. For this reason enzyme preparations are diluted so that not more than 35 mg. (44%) of the starch will be hydrolyzed in the allotted time. Kjeldahl<sup>21</sup> advised a 40 per cent limit of hydrolysis and Evans,<sup>16</sup> 30 percent.

*pH Optimum.* With some variation previous workers have found the pH optimum for amylase to be around neutrality.<sup>22, 23, 21</sup> At 37° C. we find the optimum to be at pH 7.4 (Fig. 5). Amylase, therefore, appears to be one of the few enzymes commonly found in the serum which exerts maximum activity at precisely the normal pH of blood.

*Effect of Temperature.* Roberts<sup>2</sup> found a flat range from 30 to 35° C. for the optimum of amylase activity. Kjeldahl<sup>21</sup> reported an optimum temperature of 48° C. and O'Donovan<sup>24</sup> described a "marked reduction" in activity after the enzyme was heated to 58° C. for 30 minutes. The temperature-

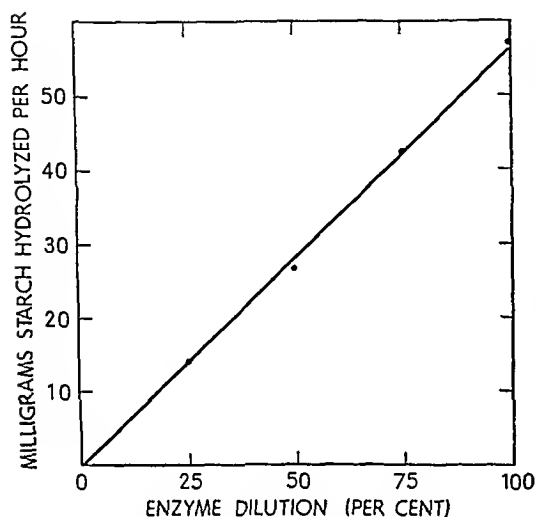


FIG. 3.—Effect of enzyme concentration on the rate of hydrolysis.

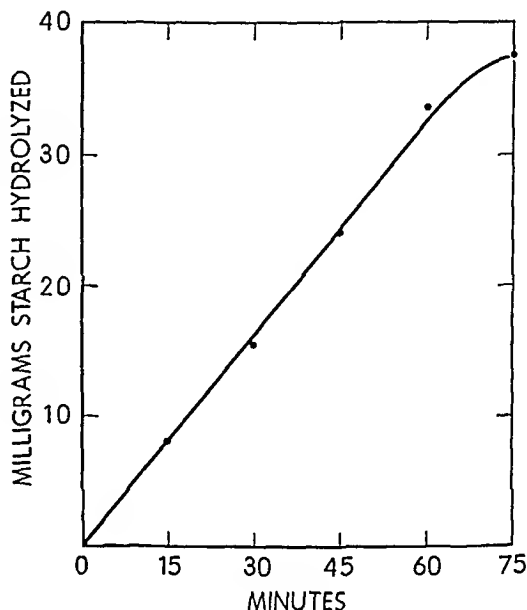


FIG. 4.—Time course of hydrolysis. The velocity decreases when the enzyme is no longer saturated with substrate.

activity curve, determined by our method (Fig. 6), puts the optimum temperature at 55° C.

*Activators and Inhibitors.* Activation of amylase by chloride ion has been observed by several investigators.<sup>3, 22, 25-29</sup>

The activity of dialyzed saliva is increased 3.8 times with sodium chloride in 3.42 millimolar final concentration. We have tested no smaller concentrations; however, the effect of increasing concentrations of sodium chloride is shown in Table 1. Wohlgemuth<sup>30</sup> observed activation in as low concentrations as 0.16 millimoles per liter (0.00097 per cent). The normal blood salt concentration of 105 millimoles per liter makes addition of salt unnecessary in an assay of undiluted sera. With dilution, however, we have found that the activity of serum falls off more than the calculated amount because of the fall in concentration of the chloride ion activator.

Enzyme samples with activity greater than that required to hydrolyze 35 mg. of starch per ml. of enzyme per hour must be diluted. To preserve

maximum activity dilution is performed with 0.9 per cent sodium chloride.

Activation of amylase by other substances, such as whole blood and tissue extracts, has been studied by Wohlgenuth<sup>31</sup> and O'Donovan.<sup>24</sup> This activity has been at least partly traced to proteins and amino acids by Rockwood<sup>32</sup> who also was the first to quantitatively determine the inhibiting effect of fluoride ion.<sup>27</sup> We have made use of the fluoride effect to inhibit the enzyme at the end of the incubation period, since acid inhibition precipitates the proteins in the enzyme sample carrying some color out of solution. A combination of fluoride ion inactivation, reduction to room temperature, and dilution are sufficient to stop the reaction. Fluoride ion is included in the Iodine Reagent described below.

TABLE I  
*Effect of Sodium Chloride Concentration on  
Amylase Activity of Dialyzed Saliva*

Final Concentration of Sodium Chloride		Relative Amylase Activity in Percent
Millimoles per liter	Percent	
0	0	26.4
0.00342	0.02	100.0
0.00684	0.04	99.0
0.01710	0.10	83.2
0.03420	0.20	85.4
0.06840	0.40	85.8
0.13680	0.80	59.8
0.25650	1.50	76.2
0.42750	2.50	48.0
0.85500	5.00	42.1
1.71000	10.00	14.1

#### METHOD

##### *Reagents*

**STARCH SOLUTION.** A 2% stock solution is freshly prepared for each series of determinations. Weigh approximately 2 gm. of starch\* in a 100 ml. beaker and suspend this starch in about 25 ml. of distilled water. Bring about 60 ml. of distilled water to a boil, pour rapidly into the starch suspension and transfer the contents quantitatively to a 100 ml. volumetric flask using hot water for washing. On cooling make the flask to volume with distilled water. This procedure yields 100 ml. of a 2% starch solution which is dissolved and almost water clear.

\* The starch which we have found most valuable is Takamine Soluble Starch manufactured by Takamine Laboratories, Clifton, New Jersey.



**Iodine Reagent.** This is a solution of 0.01 Normal Iodine containing Potassium Iodide (0.3%) and Potassium Fluoride (5%). Weigh 13 Gm. of Iodine into a weighing bottle. Dissolve, according to the method described by Van Slyke,<sup>33</sup> about 30 Gm. of pure potassium iodide in about 250 ml. of water and transfer the iodine quantitatively from the weighing bottle to a 1 liter volumetric flask washing with the iodide solution. Add the remainder of the iodide solution to the liter flask and dilute the contents to the mark. This 0.1 N stock solution is standardized by titration with a standard sodium

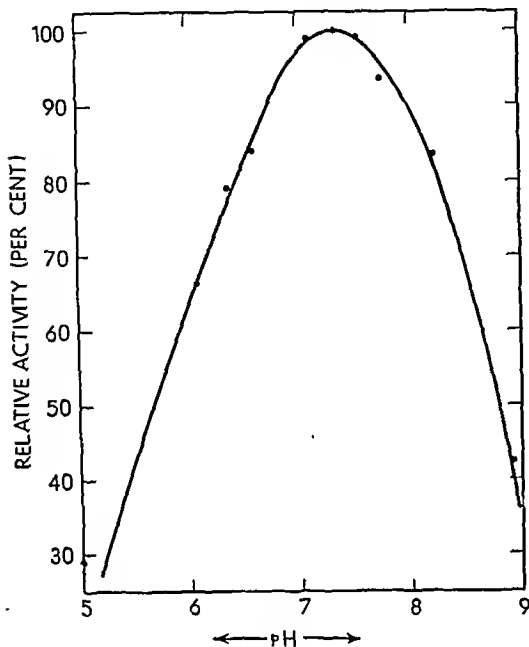


FIG. 5.—Effect of pH on the rate of starch hydrolysis by amylase. Activity is expressed in terms of per cent of the maximum.

thiosulfate solution using a starch indicator; a deviation of 0.005 N is permitted. To make the final iodine solution 50 Gm. of potassium fluoride is weighed out and added to a 1000 ml. flask containing 100 ml. of the stock iodine solution and the contents diluted to the mark.

This reagent is kept in a cool place in the dark or in a darkened bottle. Slow loss of iodine will occur but is not noticeable by titration with sodium thiosulfate for 3-4 weeks. If few determinations are to be made, it should be prepared in smaller quantities.

**Phosphate Buffer.** 0.04 M Sorensen's phosphate buffer, pH 7. Dissolve 3.471 Gm. anhydrous  $\text{Na}_2\text{HPO}_4$  and 2.118 Gm.  $\text{KH}_2\text{PO}_4$  in 1 liter of water.

**The Standard Starch-Iodine Curve.** Into each of a series of 100 ml. flasks containing 4 ml. of the iodine reagent is delivered progressive amounts of starch from 0.1 to 4.0 mg. Each flask is made to the mark and a sample of the contents is read in the Evelyn colorimeter in standard colorimeter tubes with a 660 millimicron filter.

The colorimeter readings plotted logarithmically against starch content will give a straight line which is used as the standard curve in all determinations. The concentration of the starch solution is checked daily before each test: Dilute 1 ml. of freshly prepared starch reagent to 100 ml. and compare the colorimeter reading of 5 ml. of this diluted starch in a 100 ml. volumetric flask containing 4 ml. of iodine reagent with the standard curve corresponding to 1 mg.

**The Assay Procedure.** Determinations are done in duplicate, tubes being incubated at 37° C. for one hour. For each sample to be assayed deliver 5 ml. of phosphate buffer and 4 ml. of starch solution into rimless test tubes and

stopper. For each tube prepare two 100 ml. flasks, each containing 4 ml. of the iodine reagent. Bring the test tubes to constant temperature in a stirred thermostatic bath at 37° C. Add 1 ml. of enzyme solution, appropriately diluted, from a blowout pipette to each tube; restopper the tube and invert to mix. Then immediately remove 0.5 ml. and transfer to one of the volumetric flasks; swirl the contents to assure maximal inactivation of the enzyme by fluoride ion.

Another 0.5 ml. sample is taken after one hour of incubation and treated

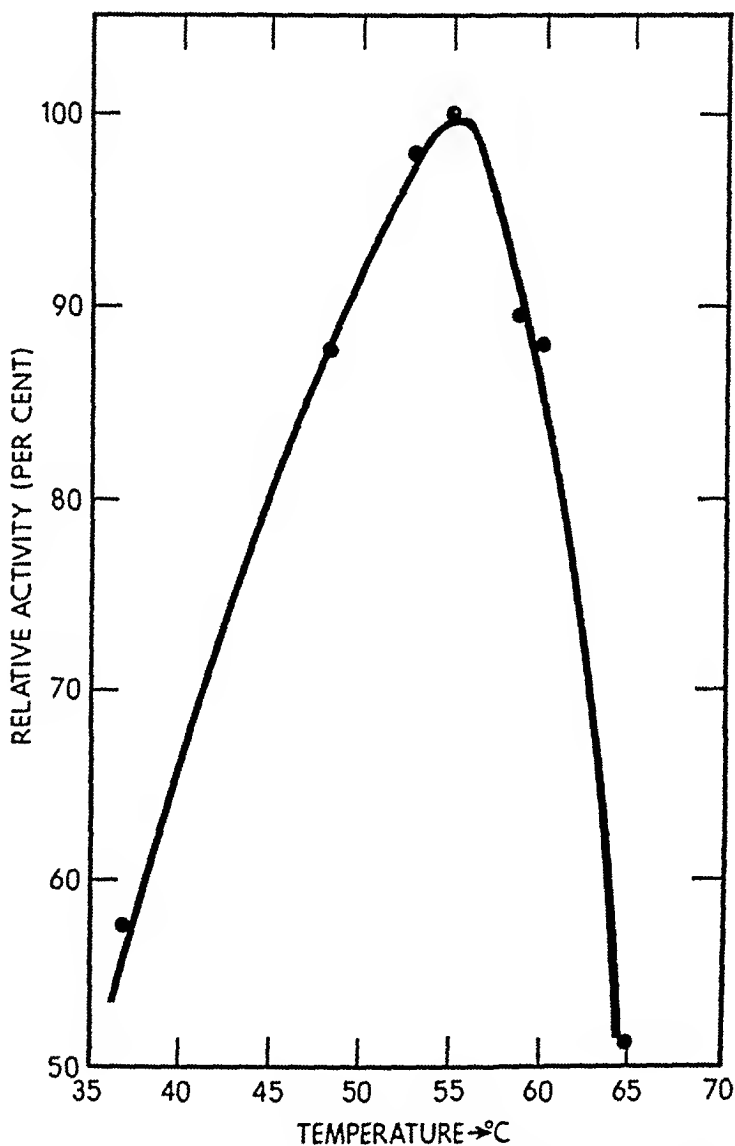


FIG. 6.—Effect of temperature on amylolytic hydrolysis.

similarly. The contents of the flasks are diluted to the mark with distilled water and an appropriate quantity is transferred to colorimeter tubes and read in a colorimeter with a 660 mu filter.

From the standard curve the amount of starch present in the aliquot removed before and after incubation is found. The initial aliquot is 1/20 of the total incubating volume and the final 1/19. Therefore, to find the

changes of total starch present in the incubating tube the initial figure is multiplied by 20 and the final by 19.

Results are expressed as units. One unit is that amount of enzyme which hydrolyzes 1 mg. of starch in 1 hour at 37° and pH7 in phosphate buffer provided that not more than 44% of the starch is hydrolyzed. In this paper units are expressed per 1 ml. of enzyme. Preparations of low activity may be incubated longer and a corresponding factor employed. Strong preparations with activity above 35 units must be appropriately diluted with 0.9 per cent sodium chloride as described above.

### RESULTS

*Normal Values.* It has been reported<sup>34</sup> that normal human serum amylase levels vary as much as 200 per cent from one individual to another.

In a series of 50 normal persons values by the present method ranged from 9.2 to 34.9 units. The average of these figures was 18 units; standard deviation  $\pm 5.32$ . No variations with sex or age were found. Multiple analyses of a given individual, examined at different times, gave more constant results, usually remaining within 10 units of one another.

Random urine samples varied in activity from 24.3 to 76.2 units with an average of 52.8. Dehydration, by limiting fluid intake, causes a rise in urinary amylase concentration which closely parallels the rise in urine specific gravity. Diuresis has the reverse effect. The dependence of amylase excretion on renal function has been repeatedly demonstrated.<sup>7, 25, 28, 35, 36</sup> Our limited experience with nephritic specimens supports the findings of these authors, that amylase activity is increased in the serum and decreased in the urine with decreased renal function.

Serum amylase levels were studied more thoroughly in one specific disease, diabetes mellitus. Much work has been reported on this subject using all amylase methods. Opinion has extended from that of Myers and Killian<sup>7</sup> who observed a significant increase in the serum, to that of Somogyi<sup>37</sup> who found a decrease in 33.4% of 382 diabetic sera to a level equalled by only 4.1% of a similar normal group. With our method we have been able to confirm the observation of Somogyi that the amylase values in diabetes mellitus are usually abnormally low. Thirty-six diabetic sera had an average activity of 13.8 units with a standard deviation of  $\pm 3.61$ .

### SUMMARY

A simple accurate colorimetric method for the determination of amylase is described and the kinetics of starch hydrolysis by amylase as measured by this method are presented. The finding of a reduction in serum amylase in diabetes has been confirmed as an example of an application of this technique.

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# SURGICAL EXPERIENCES WITH EXTRAMEDULLARY TUMORS OF THE SPINAL CORD \*

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PHILADELPHIA, PENNA.

THE PROGNOSIS FOLLOWING SURGERY in certain types of tumors of the spinal cord may be excellent. Those tumors in which the predominating cell type is a fibroblast, the meningiomas and fibroblastomas, do not invade the substance of the cord. Being attached to the adjacent meninges, they affect the cord by compression only. If they can be removed together with their attachments to the dura, arachnoid, or adjacent nerve sheaths, recurrence does not take place. And if surgical extirpation can be accomplished before irreversible damage has been done to the cord, impaired function will return to a remarkable degree. It is with this group of tumors, the intradural, extramedullary, fibroblastic tumors, their diagnosis, localization, and the results of surgical removal that this communication deals.

Since 1924, 108 tumors of this type have been recorded in the Neurosurgical Service of the University and Postgraduate Hospitals of the University of Pennsylvania and have been followed in the Tumor Clinic a sufficient length of time to warrant inclusion in this report. Of these 108 tumors, 78 were found in females, 30 in males, an unexpectedly high incidence of this type of tumor in women. The average age was 45.3 years, the youngest 10, the oldest 78. Twenty-four of these cases were in the cervical area of the cord, 70 in the thoracic, 6 in the lumbar cord, and 8 involved the cauda equina. In 10 cases the tumor showed an extradural extension, nine cases being situated in the cervical area and one in the high thoracic region. The completeness with which such tumors can be removed is shown by the fact that of the nine cases known to have died since operation, only two died of a recurrence. In three instances a recurrence was suspected but reexploration showed a damaged cord, and adhesive arachnitis, but no further evidence of the original tumor. In this group of 108 cases, 44 complete cures can be reported. Tables I, II, III, and IV should be consulted. In view of the rarity of recurrence after complete removal, these total recoveries can be considered permanent.

Originally the diagnosis and localization of spinal cord tumors was accomplished on the basis of neurologic findings alone, but since the introduction of lipiodol and other oils opaque to the roentgen ray, their injection has replaced careful and repeated neurologic studies for the determination of the level of the lesion. From the neurologic and neurophysiologic standpoint, this is to be regretted. Not only does this method eliminate much of the intellectual pleasure involved in reaching a diagnosis by neurologic methods alone, but also important neurophysiologic information is

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\* Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

TABLE I  
*Spinal Cord Tumors*  
*Intradural Extramedullary*

108 Cases
Males 30
29 white — 1 colored
Females 78
Average Age 45.3 yrs.
Youngest 10      Oldest 78

TABLE II  
*Position of Tumor*

Cervical	24	} 108 Cases
Thoracic	70	
Lumbar	6	
Cauda Equina	8	
Extradural Extension Tumor	10	
9 Cervical	1 Thoracic	

TABLE III

108 Cases
115 Laminectomies
Mortality 6
Mortality % Case 5.6 — Operative 5.2
3 operated for recurrence but none found
1 operated and recurrence removed
2 operated at wrong level (too low), but reoperated and tumor removed

TABLE IV

<i>Complete Cures 44 Cases</i>				
1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.
2	4	5	2	3
6—10 yrs.	12	11—15 yrs.	10	
16—20 yrs.	2	21—25 yrs.	7	

TABLE V

*Methods Used to Confirm Level Diagnosis*

No Queckenstedt, No Oil .....	3
Incomplete Block Oil and Queckenstedt .....	6
Incomplete Block Queckenstedt, Complete to Oil .....	19
Complete Block Queckenstedt, No Oil Used .....	18
Complete Block Queckenstedt and Oil .....	62
Symptoms Increased by Lumbar Puncture .....	5

possibly being overlooked. But from the standpoint of the patient, determination of the level of the lesion by an opaque myelogram saves him time, thereby preventing further cord damage, and assures him that the laminectomy opening will be properly placed and no more extensive than is absolutely necessary. A lumbar puncture with the application of the Queckenstedt test is an essential part of the study of any spinal cord lesion. If a tumor is suspected and if the hydrodynamic reactions and chemical studies of the spinal fluid are not entirely normal, oil should always be introduced into the subarachnoid space of the spinal canal. Occasionally, as was evidenced in five cases in this series, a lumbar puncture plus removal of fluid for protein estimation and serologic studies causes a sudden increase in symptoms of cord compression. When this sequence of events occurs, immediate exploration is obviously indicated to prevent further cord damage. In our experience this aggravation of existing cord symptoms following a lumbar puncture only occurs in the presence of a tumor.

In this series of 108 cases, one or the other of these tests were applied in 105 instances. Table V shows the results. It appears that oil is the most accurate means of reaching a level diagnosis. The position of the tumors is given in Table II.

Since these lesions are all extramedullary, they are frequently in contact with or even spring from the sheath of a posterior root. Consequently root pain or a girdle sensation is a common early complaint. In 70 cases in this series, frank pain was the initial symptom and in 10 others, numbness or hypesthesia. In 28 cases motor weakness was noted as the first disability. The relation of the tumor to the dentate ligament seems to have a definite effect upon the development of symptoms. If the tumor arises from the dura anterior to the dentate, as the mass increases in size, it will be crowded against the anterior or anterolateral surface of the cord and prevented from compressing an adjacent posterior root. Consequently generalized pressure is made upon the cord and motor symptoms may predominate over sensory complaints. In 28 instances in which motor symptoms were first noted, the position of the tumor was anterior or anterolateral in 19, and posterior or posterolateral in nine. Conversely, in the 80 cases in which pain was the initial symptom, the tumor lay posteriorly or posterolaterally in 63. Of the 17 anteriorly placed tumors causing pain, 15 lay above the second thoracic segment, nine cervical and six thoracic. And of the nine cervical tumors anteriorly situated and producing pain, eight were "dumb-bell" tumors with an extradural extension along an emerging pair of spinal roots. The posterior root was involved at this point with consequent segmental pain. All tumors involving the cauda equina, eight in number, had pain as an initial symptom.

The cervical tumors comprise an interesting group. Among these 24 cases, six lesions were situated at the level of the foramen magnum. In two instances the tumors were so nearly intracranial that cerebrospinal



fluid circulation was impaired and a choking of the discs reported. Three fatalities occurred in this group. One case had already had respiratory embarrassment and although the tumor was removed, he died in a respirator. Another case died of pneumonia 72 hours postoperatively. A third case was in satisfactory condition until, on the third postoperative day, she was turned on her back and given fluid by mouth. She promptly vomited, most of the vomitus entered the trachea and she choked to death at once. In a fourth case recurrence was suspected in an anteriorly placed tumor. Reoperation after an interval of 3 years showed no recurrence but a marked arachnitis. Death occurred from respiratory failure some months later.

TABLE VI

*Tumor in Cervical Area*

## Complete Paralysis to Complete Recovery 7

Average Time Symptoms .....	22 Months
Average Time Complete Paralysis .....	10 Weeks
Average Time to Complete Recovery .....	18 Months

*Tumor in Thoracic Area*

## Complete Paralysis to Complete Recovery 9

Average Time Symptoms .....	26 Months
Average Time Complete Paralysis .....	6 Weeks
Average Time to Complete Recovery .....	14 Months

## No Postoperative Improvement 13

Average Time Onset Symptoms .....	34 Months
Average Time Complete Paralysis .....	7 Months
Average Time Follow-up—2 yrs. ....	5 Dead

*All Tumors in Thoracic Area*

A fifth case lived a semi-invalid existence for 6 years and was reported to have died of heart failure. The sixth case is alive 3 years postoperatively and has made a complete recovery. In the postoperative care of a patient who has had a tumor removed from the uppermost levels of the spinal cord, respiratory paralysis is an ever present danger. A respirator should always be in readiness, or at least a laryngoscope or other necessary instruments for tracheal intubation. The immediate, postoperative passage of a stomach tube is a wise precaution to keep the stomach empty and to provide measured nourishment. These patients should be nursed in the prone position on a cerebellar frame so that all secretions can drain freely.

A problem not infrequently encountered in spinal cord surgery is the completely paralyzed patient. Is operation worthwhile under such conditions? What criteria do we have to indicate the advisability of surgical intervention? Sixteen cases, seven in which the tumor was located in the cervical area, and nine in which the tumor was in the thoracic area, had total spastic paraplegia of the legs, loss of sphincter control, and a complete or almost complete sensory loss below the level of the tumor. In the cervical group of

tumors, (7) the average period from the onset of symptoms to the operation averaged 22 months; the period of complete paralysis averaged ten weeks. In the thoracic group of tumors, (9) the average time of duration of symptoms was 26 months, and of complete paralysis, six weeks. Yet all these cases made complete recoveries; the cervical in an average time of 18 months after tumor removal, the thoracic after 14 months. All have resumed work. Thirteen other cases were completely paralyzed and showed no postoperative improvement. The average duration of symptoms prior to surgical intervention was 34 months, and with complete paralysis, seven months. The average follow-up time in this unimproved group is two years. Five are known to be dead. All these tumors were located in the thoracic area with a single exception in the cervical region. It seems evident, therefore, that a case with a spinal cord tumor who has been completely paralyzed for two months has better than an even chance for recovery, if the tumor can be removed without further damage to the cord. (Table VI.)

In this group of 108 cases, six are postoperative deaths, 44 are completely cured, and 13 completely paralyzed, five of whom are known to be dead. What of the 45 cases remaining that do not fall into any of these categories? Four are known to be dead of intercurrent disease. Twenty-eight are improved, but not working, 16 are unimproved with the same partial disability as they had before the tumor was extirpated.

#### CONCLUSIONS

A tumor within the spinal canal, intradural and extramedullary in position, has a definite clinical history, pain, paresthesia, paralysis. Segmental pain is the first symptom, followed by sensory change and slowly developing motor weakness below the level of the lesion. The presence of a tumor should be expected if interference with cerebrospinal fluid hydrodynamics and chemical components can be demonstrated. Confirmation of the diagnosis and determination of the level of the lesion can be had by the injection of opaque oil. Unless the symptoms of cord compression have been allowed to progress unchecked for too long a period, the chances for improvement or even a complete cure, following surgical removal of the tumor are excellent.

DR. GILBERT HORRAX, Boston: I think Dr. Grant has done well to call our attention to these tumors and to summarize his experiences with a series of cases over a long period. Most of us have realized that extramedullary spinal cord tumors are extremely favorable tumors. I think Dr. Grant has brought out one fact very clearly; that is, that even though patients have had paralysis for a long time they are still capable of coming back to a perfect, or nearly perfect, result. In our series we have had 60 patients with 61 tumors—one had two tumors, which is rather unusual—and our statistics agree almost entirely with his as to sex and age and so on, the great majority being females and the age range running from 18 to 71. We also have used in recent years in a large proportion of the cases, some contrast medium to designate the level of the growth more distinctly than could be found by neurologic means. We have used oxygen a good many times, but also lipiodal or pantopaque.

(Slides) We have had what we would call good or excellent results in 44 cases, 72 per cent. These end results are, with a few exceptions, for a period of about four years. I am quite sure that when we get a complete followup our good or excellent results will be improved, because I think as years go on there will be further improvement; that seems to be one characteristic of these tumors, that improvement comes over a period of years, not just over a few months. We had one death in this group, and one case we could not follow.

This chart is interesting. There were 45 neurofibromas. On a purely arbitrary basis I have taken cases which had symptoms for twelve months or less to see whether duration of symptoms had any relation to results. In 85 per cent of patients who had symptoms for less than a year we had good or excellent results, but of those with symptoms for as long as five years with severe pain or paralysis, there were no good results. It is possible that an occasional case will show a better result over a period of years. On the other hand, if the weakness had not gone on to paralysis we had some with excellent recovery.

That is really about all there is to say from my standpoint, except to remark that surgeons in general and neurosurgeons in particular have recognized that they are very favorable tumors, ever since Sir Victory Horsley took out the first one in 1887, in which he got a perfect result. I think Dr. Grant has been very wise in studying this series so that he would know exactly what the situation was and how well they did, sometimes coming from complete paralysis to a perfect result.

# THE CONTROL OF ANOXEMIA DURING SURGICAL ANESTHESIA WITH THE AID OF THE OXYHEMOGRAPH\*

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IN A 1939 PRESENTATION to the American Surgical Association, entitled "Anoxia—A Source of Possible Complications in Surgical Anesthesia," McClure and associates<sup>1</sup> reached the conclusion that, "Full consideration of anoxia as a source of surgical complications should reduce preoperative narcotics to a minimum, promote the use of anesthetics which allow adequate oxygen in the inspired air, and emphasize the necessity of maintaining the blood pressure and respiration at near normal levels." "Further Anesthesia Studies with the Photoelectric Oxyhemoglobinograph"<sup>2</sup> were presented to this association in 1940. This communication emphasized the fact that the slow laborious method of following the oxygen saturation of the blood by means of repeated arterial punctures and gas analyses was not a practical procedure for clinical work especially as applied to anesthesia where immediate minute to minute results were essential for the guidance of the surgeon and the anesthetist in the prevention of operative and postoperative complications associated with anoxia. The application of the photoelectric cell technic, as suggested by Kramer<sup>3, 4</sup> and Matthes<sup>5, 6</sup> in 1934 and 1935 in experimental procedures, was described in the use of an imported Kramer apparatus and an instrument of our own construction which was a complete innovation including a vacuum type photocell, radio amplification and ink recording. The possibility of employing the photoelectric technic for blood oxygen saturation in clinical work by means of the portable, sensitive oxyhemoglobinograph was demonstrated for the first time.

In medical and dental practice the fields of narcosis and anesthesia are obviously the ones where most can be done in the prevention of anoxia. Closely allied and frequently associated is the shock syndrome which usually implies severe anoxia.

Although the exact mechanism of narcosis remains controversial, the logical approach seems to be that of Warburg<sup>7</sup> and Quastel<sup>8</sup>—tissue respiration. The recent work of Schmidt<sup>9</sup> and Himwich<sup>10</sup> and their associates on pentothal anesthesia suggests that a part of the narcotic mechanism is a histotoxic anoxia, as demonstrated by a depression of the cerebral cellular respiration. If this theory of narcosis is accepted, it is obvious that some degree of anoxia may be an inevitable complication of anesthesia. The objective of the anesthetist, then, is to control anoxia within safe reversible limits in order to avoid irreversible pathological changes on the one hand and light narcosis with increased hypersensitivity on the other.

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\* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

The successful control of anoxia depends primarily on its prevention or early detection. Of the four types of anoxia, the one most readily recognized is anoxic anoxia, i.e., anoxemia. It is caused by an impaired oxygenation of the arterial blood at the lungs and is characterized by cyanosis and a generalized oxygen lack in all the tissues of the body. The occurrence of arterial anoxemia during anesthesia has been confirmed through objective observations as well as by chemical analyses.

It is an established fact that the human eye is subject to inaccuracies in so far as visual impressions of color are concerned. The interpretation of color varies not only from one individual to another but also in the individual response to the same color at different times. The development of photoelectric methods has afforded a means of proving this point conclusively. Comroe and Botelho<sup>11</sup> have recently reported that visual impressions of cyanosis are unreliable. They evaluated the ability of observers to detect cyanosis in 20 normal males, subjected to various gas mixtures, by a comparison of their color estimations with known arterial oxygen saturations, as obtained photoelectrically with the Millikan oximeter. Cyanosis was not detected by the majority of the 127 observers until the blood oxygen saturation fell to approximately 80%; while 25% of the observers were unable to recognize cyanosis even when the arterial oxygen saturation fell to levels of 71-75%. The authors point out that serious grades of arterial anoxemia may pass unrecognized by many physicians unless arterial blood is analyzed for oxygen content and capacity.

In the light of these findings, it is clear that the anesthetist requires instantaneous and accurate information concerning the degree of arterial oxygenation of the patient, if he is to fulfil his objective. Chemical analysis, which is a tedious and time-consuming procedure, offers no immediate aid. Consequently, he has had to rely on the changing color, blood pressure and pulse of the patient. The photoelectric oxyhemograph, recently described by Hartman, Behrmann and Chapman<sup>12</sup> should solve this problem for the anesthetist and allow him to supplement his observations with an accurate, continuous record of arterial blood oxygen.

It is the purpose of this presentation to describe the development of the oxyhemograph briefly and to show data which will prove the value of the instrument in the control of anoxemia in anesthesia.

Although the first photoelectric estimation of oxyhemoglobin is attributed to Nicolai<sup>13</sup> in 1932, the fundamental work in blood oximetry was performed by Kramer<sup>3, 4</sup> and Matthes<sup>5, 6</sup> each working independently. Kramer recorded variations in oxyhemoglobin *in vitro* and *in vivo*, using a method based on the spectral differences of hemoglobin and oxyhemoglobin in the red wave length region (620-770 mμ). He showed that Beer's law of optical absorption may be applied to hemoglobin solutions and hemoglobin in the red cell. Matthes' contribution was the continuous registration of light absorption in different spectral regions, using red light for oxygen content

and green light for the total hemoglobin. In 1935 Matthes<sup>6</sup> adapted Kramer's method<sup>4</sup> for closed blood vessels in the experimental animal to human beings, using an ear lobe attachment.

After using an imported Kramer apparatus, Hartman and McClure<sup>2</sup> developed a one-color instrument which operated in the red wave length region. This "oxyhemoglobinograph" consisted of a photoelectric colorimeter in which the beam of light passed through the web of the hand. Although the apparatus provided the desired sensitivity for clinical studies, its most serious limitation arose from volume changes in the tissue thickness exposed to the light beam, thus introducing an error.

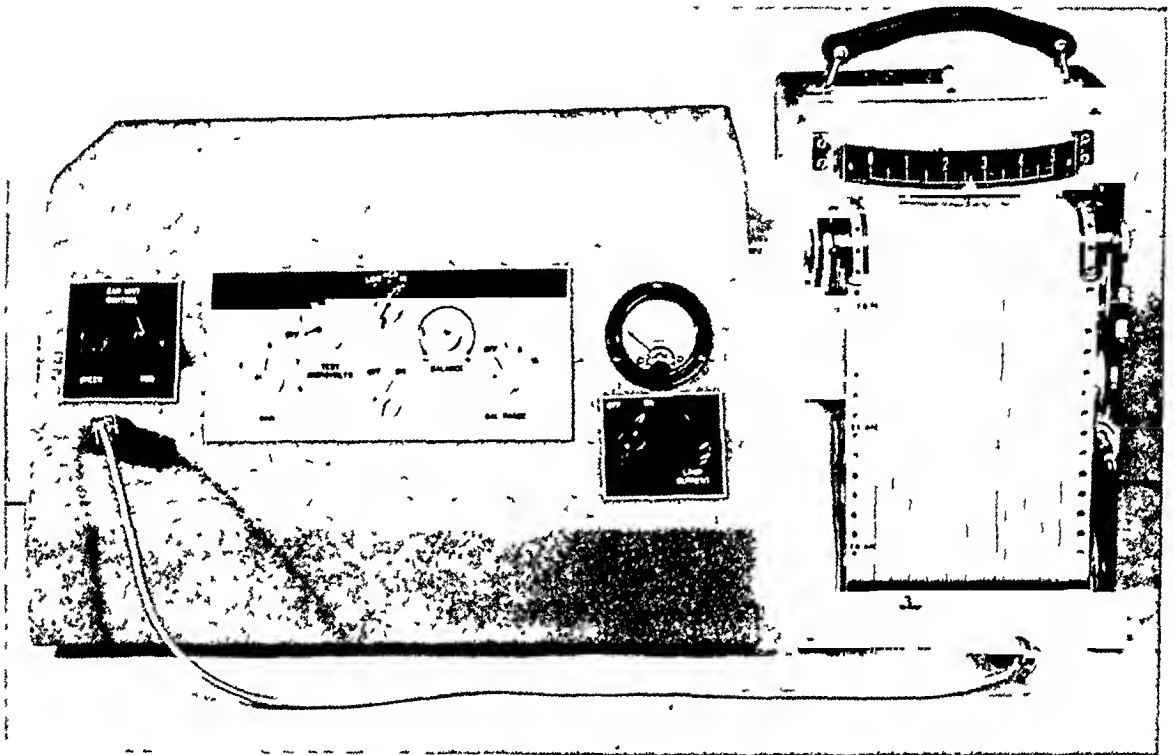


FIG. 1.—The oxyhemograph.

Matthes<sup>5</sup>, Squire<sup>14</sup>, Goldie<sup>15</sup>, and Millikan<sup>16</sup> have appreciated the disturbance created by volume variations and have attempted to correct for it in their photoelectric methods for blood oxygen determination. Although the technical details vary, all of these methods involve photocell recordings in two spectral regions, one sensitive to total hemoglobin (near infrared, Squire; blue, Goldie; green, Matthes and Millikan) and the other, the red wave length, which is sensitive to oxyhemoglobin. Squire and Goldie standardized their instruments by rendering the tissue bloodless, whereas Millikan compared the fully flushed ear with an optical filter. Of these three methods, only the Millikan oximeter reached the production stage and, therefore, it was used extensively in the war-time aviation research program.

The oxyhemograph (Fig. 1) has incorporated within it the best features of the technics described in earlier publications. It is the result of the joint endeavor of workers from the Department of Laboratories, Henry Ford Hospital, and the Research Laboratories Division, General Motors Corpora-

tion, Detroit, Michigan. The blood oxygen saturation is measured through the use of a bichromatic photocell as registered through the ear, a unique feature of the method being the amplification by means of a "contact-modulated" D.C. amplifier, which is stable and sensitive and allows a permanent, continuous record on a rugged D.C. milliammeter.

The ear unit\* (Fig. 2) contains two miniature photocells, a small lamp,

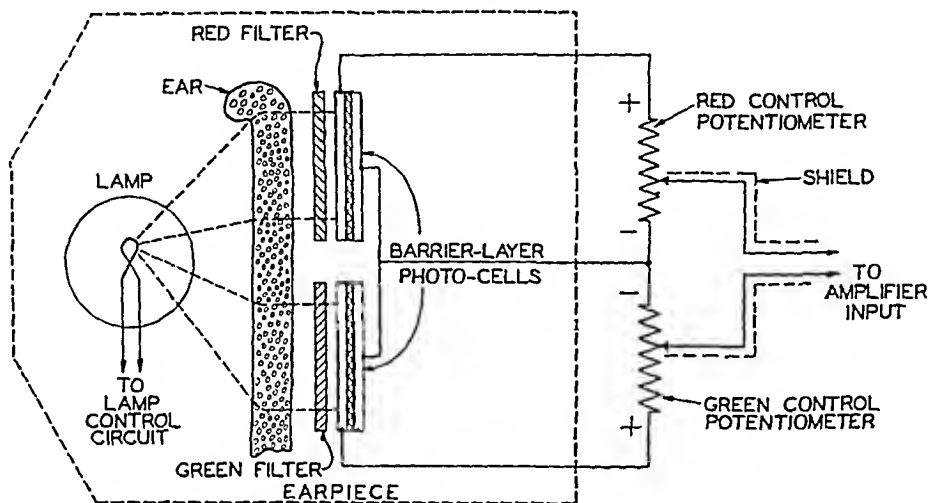


FIG. 2.—Circuit diagram of the photo-electric ear-piece and control potentiometers.

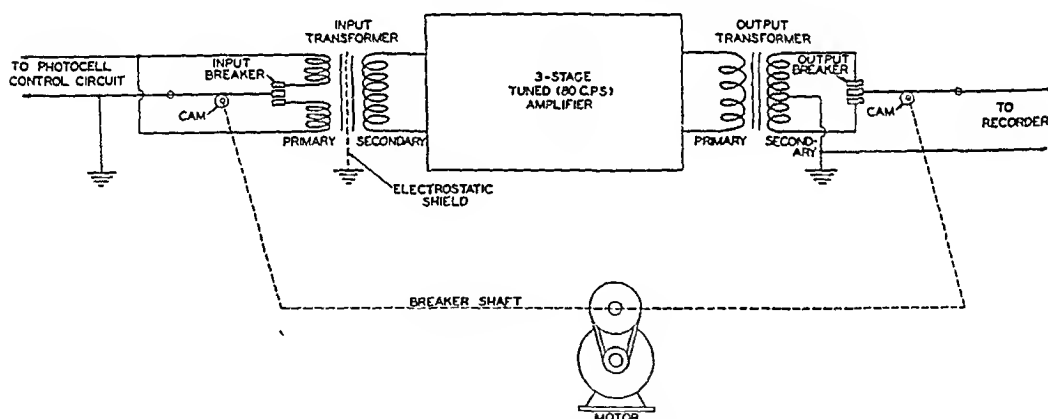


FIG. 3.—Block diagram of the amplifier unit.

and two color filters. Light transmitted through the ear is measured in two spectral regions. The "red" cell photocurrent reflects changes in the oxygenation of the blood together with volume variations.\*\* The "green" cell photocurrent reflects only volume variations because in this spectral region

\* Coleman Electric Co., Maywood, Ill.

\*\* The expression "volume variations" includes four variables: (1) tissue thickness which affects the amount of light absorption by the tissue itself; (2) extent of the capillary bed which affects the amount of blood in the optical path; (3) total hemoglobin which affects the amount of hemoglobin in the optical path; and (4) vasomotor changes, caused by fluctuations in blood pressure which would affect factor (2), and associated at times with a redistribution of hemoglobin, as may occur in shock, which would affect factor (3).

the absorption characteristics of oxyhemoglobin and reduced hemoglobin are similar. The two photocurrents are opposed to one another so that changes due to volume variations are largely canceled out, allowing only the signal measuring an oxygen change to be emitted. This difference signal is changed to alternating current, is amplified, rectified and sent to a milliammeter which makes an ink record of blood oxygenation (Fig. 3).

The instrument was calibrated by correlating actual arterial blood oxygen saturation values with the oxyhemograph readings (Fig. 4). The blood was analyzed in duplicate for oxygen content and oxygen capacity, using Van Slyke's manometric method. The per cent saturation was computed from

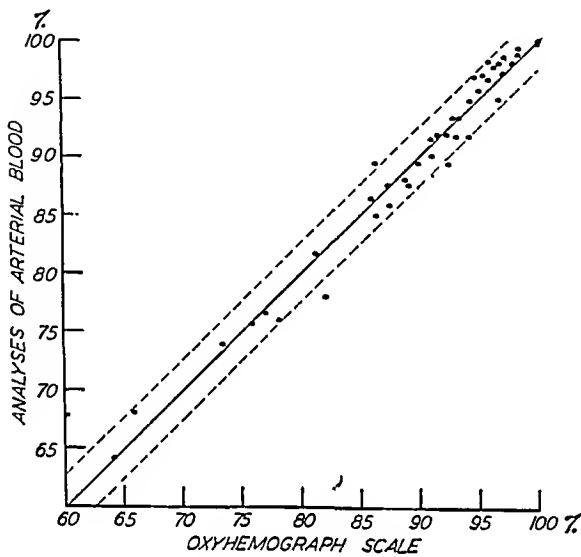


FIG. 4.—Correlation between the chemical and instrumental values for the blood  $O_2$  sat. in %. Identical value fall on the solid line. 28 out of 42 points (66.6%) lie within  $\pm 1\%$ . Those points (39 out of 42 or 92.8%) included within the broken lines represent an agreement of  $\pm 2\frac{1}{2}\%$ . The remaining points (3 out of 42 or 7.2%) are within 3-8%.

these figures. Data obtained on 20 patients under pentothal— $N_2O$ — $O_2$  anesthesia show that the chemical and instrumental data are usually within  $\pm 2\frac{1}{2}\%$ . The conformity of the blood values and the oxyhemograph are proof of its reliability.

The sensitivity of the oxyhemograph permits a tracing of the fluctuations in the oxygenation of the blood associated with the respiratory cycle. This is well demonstrated not only in the experimental animal (Fig. 5) but also in the anesthetized human (Fig. 8). Such a rapid response should make the instrument a boon to the anesthetist, for the first warning of developing anoxemia is registered much earlier than can be appreciated by clinical observations.

Oxyhemography was employed in a series of operations requiring one half to ten hours of anesthesia. Each record included blood oxygen saturation curves during the preanesthesia period in room air, the induction, and the fluctuations, occurring throughout the surgical anesthesia. Records were obtained under various types of anesthesia, as follows: pentothal, pentothal— $N_2O$ — $O_2$ , cyclopropane, ethylene and ether, and spinocaine anesthesia.

#### PENTOTHAL

The current widespread usage of intravenous anesthesia, together with the variance of opinion as to the necessity for coincident oxygen administration, prompted the early work carried out with the oxyhemograph. It seemed that a continuous record of blood oxygen should offer information, otherwise impossible to obtain under the short-acting barbiturates. As the study progressed, the combination of pentothal— $N_2O$ — $O_2$  was included because



of its extensive use in surgical anesthesia. Both experimental\* and clinical subjects were used in these studies.

Clinical data was acquired on 20 orthopedic cases, subjected to pentothal, pentothal —  $O_2$ , or pentothal —  $N_2O$  —  $O_2$  anesthesia, of a duration ranging from 17 to 218 minutes. The preoperative medication consisted of  $\frac{1}{4}$  to  $\frac{1}{6}$  gr. of morphine sulfate and  $\frac{1}{150}$  gr. of atropine sulfate. The pentothal was administered by the intermittent technic of Lundy and varied according to the individual's sensitivity to the drug. The total dose ranged from  $\frac{1}{2}$  to  $1\frac{3}{4}$  gms. The inhalation anesthesia was administered by face mask in the usual manner. Although a 50-50  $N_2O$ - $O_2$  mixture was preferred, the effects of altering the ratio of  $N_2O$  to  $O_2$  on the blood  $O_2$  curve were obtained. Two arterial punctures were obtained during the anesthesia for calibration of the curve. Gas samples were drawn from the rebreathing bag for analysis to verify the  $N_2O$ - $O_2$  mixture administered.

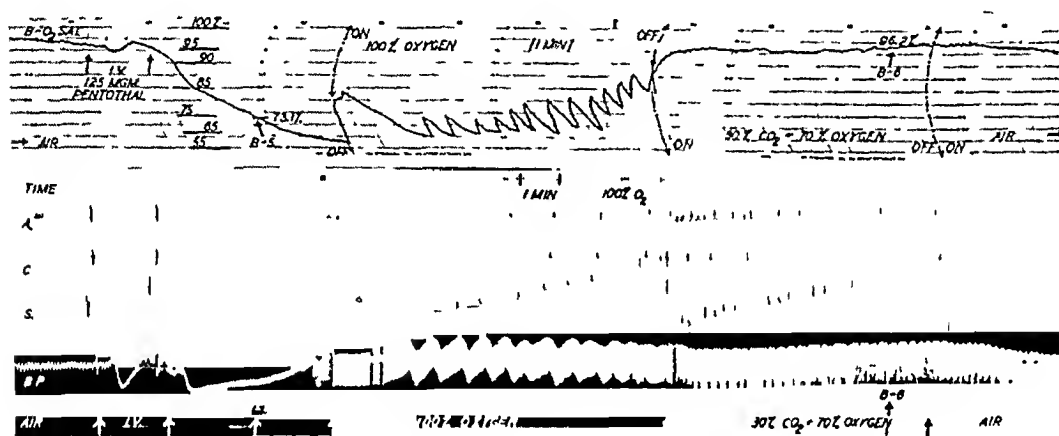


FIG. 5.—Simultaneous tracings of blood  $O_2$  saturation in % (B— $O_2$  sat.) time in fifths of a minute, abdominal (A) and costal (C) respiration, spirometer (S) record of pulmonary ventilation and blood pressure (B.P.) on a dog, subjected to pentothal anesthesia are shown. (B-5) and (B-6) represent analyses of arterial blood. An intravenous (i.v.) injection of 125 mgm. of pentothal under room air conditions caused a cessation of the respiration which created a marked decrease in the blood  $O_2$  saturation from 97% to 52%. The slow recovery of 100%  $O_2$  is graphically depicted by the tracings. As the expiratory phase of each respiratory cycle is completed, an immediate upward swing of the oxyhemograph pointer to a peak, followed by a fall until the end of the next respiratory cycle is observed. It is possible to align each wave in the tracing with a breath. The administration of a 30-70  $CO_2$ - $O_2$  mixture increased the rate and depth of the respiration, thus smoothing out the oxyhemograph tracing. On return to room air, a more regular respiration rate was able to maintain normal blood oxygenation.

A comparison of three types of pentothal inductions illustrates the value of  $O_2$  therapy in intravenous anesthesia (Fig. 6). In the bone graft case, the induction was performed in air. The blood  $O_2$  fell from 87% saturated to 68% saturated after the patient had received 16 cc. of  $2\frac{1}{2}\%$  pentothal. The insertion of the airway, followed immediately by a 50-50  $N_2O$ - $O_2$  mixture, caused the blood  $O_2$  to become 98% saturated within three minutes. Changing the mixture to a 26-74 ratio of  $N_2O$ - $O_2$  had no effect on the blood

\* To be published.

# CONTROL OF ANOEXMIA DURING ANESTHESIA

## COMPARATIVE PENTOTHAL INDUCTIONS

PREMEDICATION - MORPHINE GR. 1/8 ATROPINE 1/50

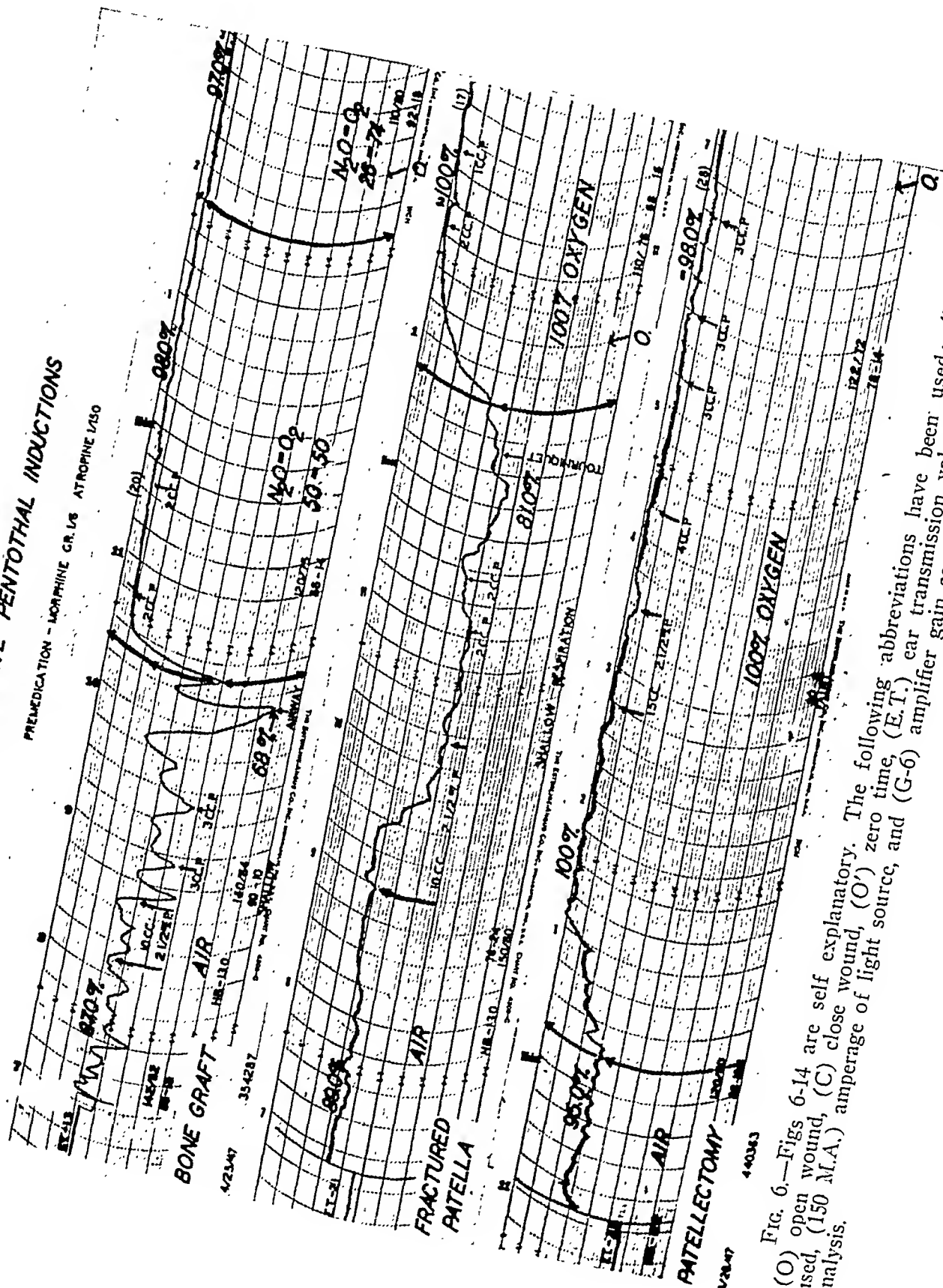


Fig. 6.—Figs 6-14 are self explanatory. The following abbreviations have been used: (P) pentothal, (O) open wound, (C) close wound, (O) zero time, (E.T.) ear transmission value, (0.5 A) type of filter used, (150 M.A.) amperage of light source, and (G-6) amplifier gain control setting, (A) airway, (B) blood analysis.

O<sub>2</sub> level. This kind of induction is probably the most common procedure used in pentothal—N<sub>2</sub>O—O<sub>2</sub> anesthesia. The second induction was carried out on a patient to be operated on for a left, comminuted fracture of the patella. The blood O<sub>2</sub> fell from 89% to 81% in air after an administration of 14 cc. of 2½% pentothal. The administration of 100% O<sub>2</sub> brought the blood O<sub>2</sub> level to 100% saturated within two minutes. The third case, a patellectomy, shows a room air blood O<sub>2</sub> value of 95% saturated, followed by the administration of 100% O<sub>2</sub>. The pentothal was not administered until the patient had breathed O<sub>2</sub> for five minutes, at which time the O<sub>2</sub> had reached a value of 100% saturated. Although 28 cc. of pentothal was necessary, the blood O<sub>2</sub> saturation showed no change, maintaining the high level of 98% to 100%. This comparison shows the definite advantage of high O<sub>2</sub> concentrations during the induction period and during the maintenance of anesthesia. The 50-50 N<sub>2</sub>O—O<sub>2</sub> mixture apparently is as efficient as 100% O<sub>2</sub> and has the advantage of reducing the pentothal requirement. It is important to reach maximum oxygenation at the beginning of the anesthesia as it is easier to maintain this level than to bring it about after a period of pentothal anesthesia.

In all barbiturate anesthesia one finds a marked variation in individual sensitivity to the drug. A 51-year-old male, a chronic alcoholic, underwent an orthopedic operation for comminuted fractures of the tibia and fibula. The preanesthesia blood O<sub>2</sub> level was 88% (Fig. 7), but after an intravenous administration of 10 cc. of 2½% pentothal the blood O<sub>2</sub> saturation fell rapidly to a value below 60%. On noting the blood O<sub>2</sub> decrease, the anesthetist put the airway in place. Then with difficulty the patient was given 100% O<sub>2</sub>, thus bringing the blood O<sub>2</sub> saturation up to 99%. The major part of the operation was performed under pentothal supplemented by a 50-50 N<sub>2</sub>O—O<sub>2</sub> mixture. The latter part of the operation shows that the blood O<sub>2</sub> was maintained at 92% saturated under a 60-40 N<sub>2</sub>O—O<sub>2</sub> mixture. Shortly after the tourniquet was removed the patient breathed room air for 7 minutes, during which time the blood O<sub>2</sub> fell to 82% saturated. Although the wound had been closed the patient was kept in the operating room for further observation since he showed early cyanosis. After 6 minutes of O<sub>2</sub> the blood level rose to 87% saturated but, with the return to room air, removal of the patient's mask and airway, the blood O<sub>2</sub> saturation fell gradually to 62% within 9 minutes. This chart indicates that sensitivity to pentothal may be observed in the induction period. It may give a warning of the amount of pentothal a patient may tolerate and may even suggest the extent of the hypoxemia in the postoperative stage.

Organe and Broad<sup>17</sup> first used the combination of pentothal — N<sub>2</sub>O — O<sub>2</sub> anesthesia to obtain relaxation that is impossible with N<sub>2</sub>O alone and to avoid the prolonged depression caused by large doses of pentothal. They used an 85-15 mixture which reduced the pentothal requirement to slightly more than half the usual dosage. At present proportions of N<sub>2</sub>O — O<sub>2</sub>

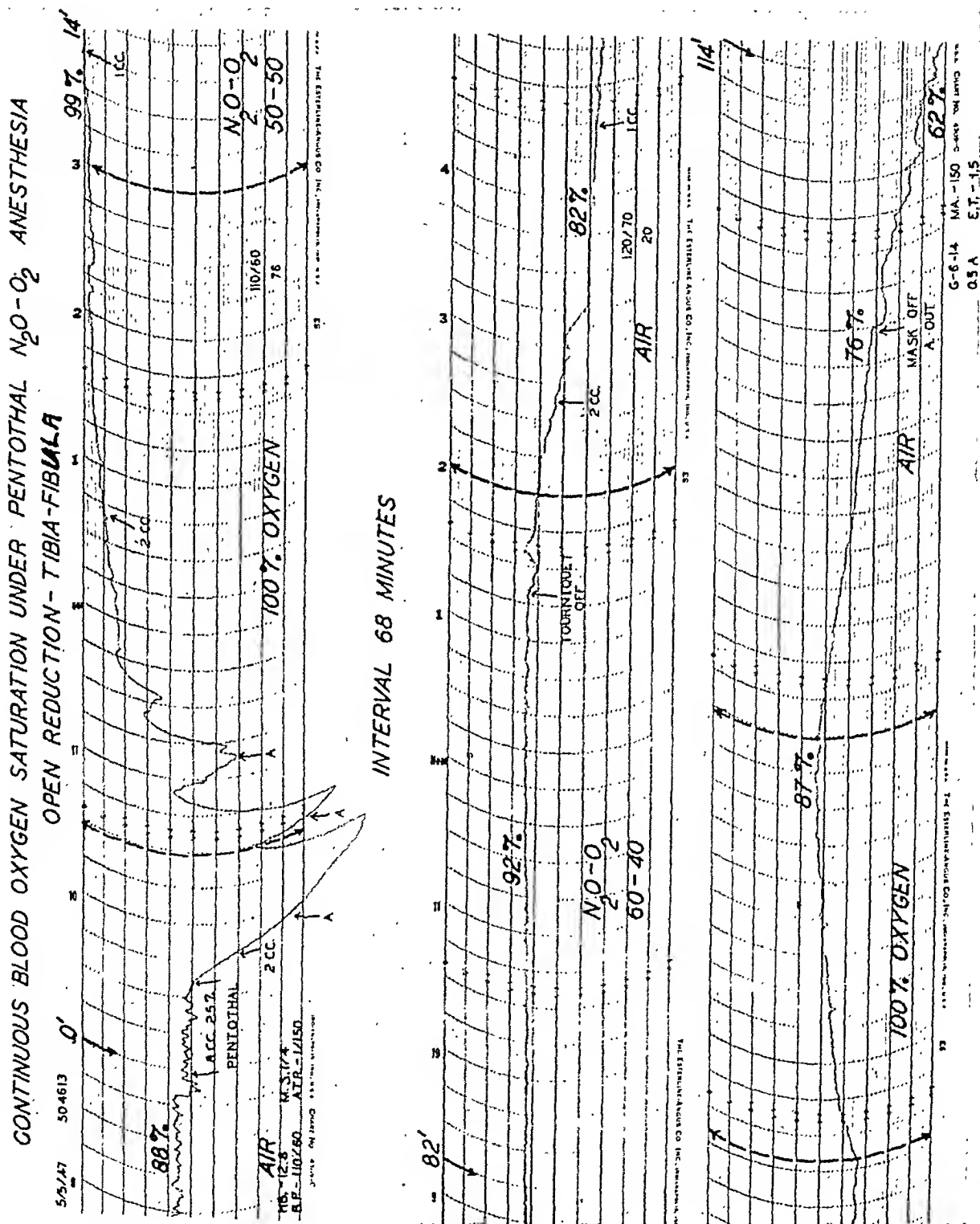


Fig. 7.  
(See Figure 6 for legend.)

ranging from 85-15 to 50-50 are in use, although the 50-50 ratio is favored for it insures adequate oxygenation as well as a reduction in the pentothal requirement. Leake and Hertzman<sup>18</sup> and McQuiston, Cullen, and Cook<sup>19</sup> have reported that  $N_2O - O_2$  mixtures alone, below the 80-20 ratio will cause extreme anoxia. Therefore, we studied blood  $O_2$  values under pentothal supplemented by  $N_2O - O_2$  mixtures in proportions ranging from (0-100) to (90-10).

The oxyhemograph tracing taken on a 44-year-old male (Fig. 8), while a patellectomy was performed under pentothal —  $N_2O - O_2$  anesthesia, gives typical data of the degree of blood oxygenation when the inspired  $O_2$  is decreased by 10% increments. The blood  $O_2$  fell from 93% to 77% in the induction period. Typical respiratory waves emphasize the sensitivity of the oxyhemograph. These fluctuations show actual changes in the blood  $O_2$  saturation coincident with each respiratory cycle. The blood  $O_2$  remained between 97% and 100% so long as the  $O_2$  in the  $N_2O - O_2$  mixture was above

TABLE I.—Summary of Blood  $O_2$  Saturation Values under Pentothal Anesthesia, Supplemented by Varying Proportions of  $N_2O - O_2$

$N_2O - O_2$ %	Number of Administrations	Range of Blood $O_2$ Values % Saturation	Average of Blood $O_2$ Values % Saturation
0-100	39	81-100	94
25-75	6	76-100	95
30-70	5	88-100	95
40-60	4	93-100	97
50-50	26	69-100	95
60-40	8	78-100	94
66-33	3	85-100	93
70-30	9	67-99	86
75-25	6	88-99	93
85-15	5	58-78	67
90-10	5	35-68	53

30%. Within the last 10 minutes of the operation the patient breathed room air for  $2\frac{1}{2}$  minutes, during which time the blood  $O_2$  fell to 93.4% saturated, as checked by an arterial puncture. The reduction of the  $N_2O - O_2$  mixture to an 84-16 ratio caused the blood  $O_2$  to drop rapidly from 97% to 64% within  $5\frac{1}{4}$  minutes. This type of curve occurred in every instance in which the  $O_2$  administration was less than 20%. At the end of this operation we obtained a graphic recording of the commonest danger of the post-anesthetic period. The patient had been breathing  $O_2$  for about one minute previous to the removal of the mask and his transfer from the operating table to the stretcher when the chin dropped and the tongue blocked the pharynx. The blood  $O_2$  fell rapidly from 97% saturated to 58% saturated within  $2\frac{1}{4}$  minutes but when the anesthetist's attention was called to this depression of the  $O_2$  record, simply lifting the patient's chin with restoration of the air passage allowed the blood  $O_2$  to return to normal. This record should prove valuable in impressing all concerned with the need for alertness in protecting the patient during the immediate postoperative period.

Table I summarizes the data on blood  $O_2$  saturation over the entire range of  $N_2O - O_2$  mixtures used in conjunction with pentothal. It is clear that in  $N_2O - O_2$  mixtures in which the  $O_2$  value is 30% or more, the blood

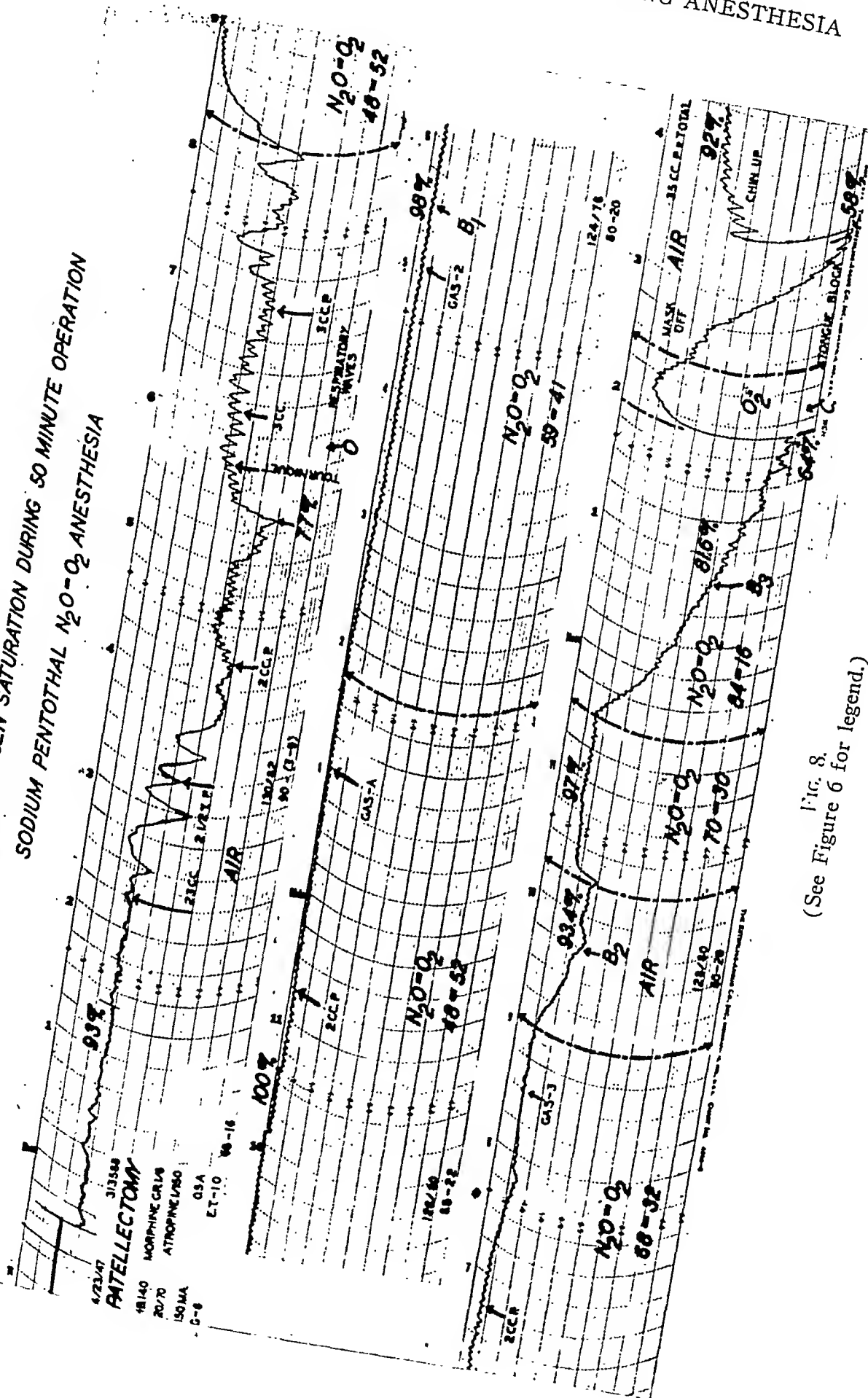


FIG. 8.  
(See Figure 6 for legend.)

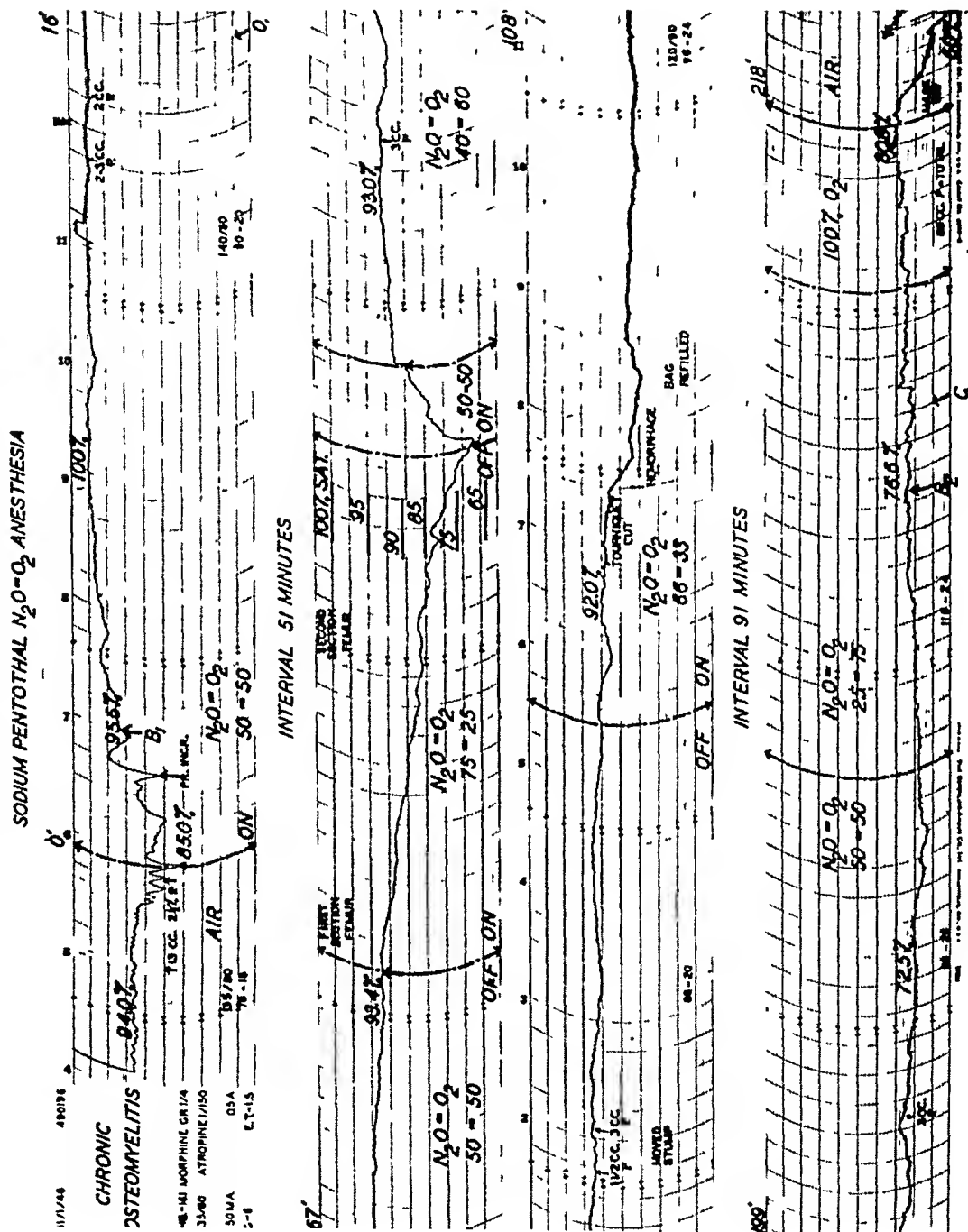


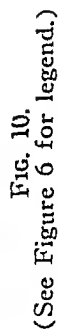
FIG 9  
(See Figure 6 for legend.)

oxygenation is maintained at 93% saturated or above. If, however, the  $O_2$  content of a  $N_2O - O_2$  mixture is 25% or less, hypoxemia appears. The average blood  $O_2$  saturation value obtained with the 75-25  $N_2O - O_2$  ratios was 86%. This is, of course, on the borderline between safe oxygenation and hypoxemia. However, it should be noted that the range of values obtained was from 67% to 99%, dependent largely upon the pentothal dosage. In the 10 instances in which the  $O_2$  inspired was 15% or less, severe hypoxemia occurred. This is proven by the fact that the entire range of blood oxygen values recorded was below safe levels. The average blood  $O_2$  saturation of 67% in the 85-15  $N_2O - O_2$  mixtures and 53% in the 90-10  $N_2O - O_2$  mixtures are definite proof that the 85-15  $N_2O - O_2$  mixtures used by Organe and Broad are too low in  $O_2$  and usually cause serious anoxia.

An analysis of the data shows that patients receiving as much as  $1\frac{3}{4}$  Gm. of pentothal over periods up to two hours, maintain a blood  $O_2$  level above 90% so long as the  $O_2$  administered is above 40%. Even 100%  $O_2$  is not adequate for normal oxygenation in operations lasting over two hours. This is well demonstrated in Fig. 9, which depicts an oxyhemograph recording during a high thigh amputation on a 23-year-old male who was suffering from chronic osteomyelitis. A normal induction, followed by the usual increase in blood  $O_2$  under a 50-50  $N_2O - O_2$  mixture, is shown. As the tracing is followed during the second hour of anesthesia, it may be noted that a 75-25  $N_2O - O_2$  mixture caused the blood  $O_2$  saturation to fall from 93% to 66% within a nine minute period. An increased  $O_2$  administration (60%) brought the blood  $O_2$  value back to 93% saturated. Toward the end of the second hour the tourniquet on the stump was released. Hemorrhage occurred and obviously some unoxygenated blood was returned to the circulation. This period is characterized on the  $O_2$  saturation record by an immediate drop in blood  $O_2$ . It is worth emphasizing that, from this point on, the blood  $O_2$  never returned to a normal level, possibly because the shock syndrome was appearing at this time. In the fourth hour of anesthesia the blood  $O_2$  was 72.5% saturated under a 50-50  $N_2O - O_2$  mixture. An increase of 25% in the  $O_2$  inspired raised the blood level to 76.6% saturated as checked by an arterial blood analysis. At the close of the operation the administration of 100%  $O_2$  increased the  $O_2$  saturation only as high as 81%. In the postanesthesia period the blood  $O_2$  fell rather sharply to 58% — 60% saturated. This anoxemia was clinically confirmed by the patient's ashen gray perspiring facies.

In  $N_2O - O_2$  mixtures containing less than 40% the blood  $O_2$  level fell below 90% after  $\frac{1}{2}$  hour of anesthesia with pentothal dosages as low as  $\frac{3}{4}$  Gm.  $N_2O - O_2$  mixtures containing less than 20%  $O_2$  caused the blood  $O_2$  to fall to 78% or lower within two-to-four minutes with pentothal administrations as low as  $\frac{1}{2}$  Gm. One exception in this series, a borderline anemia (Hb. — 10.7 Gm.) patient, showed values lower than 90% even on 100%  $O_2$  and therefore suffered severe anoxemia under the  $N_2O - O_2$  ratios containing lower  $O_2$  percentages. The patient, of course, showed no skin





discoloration for she did not have the 5 Gm. of hemoglobin in the unsaturated state essential for cyanosis at any time.

#### CYCLOPROPANE

Oxyhemograph tracings were obtained under  $C_3H_6 - O_2$  anesthesia under different types of operations. The cholecystectomy, pneumonectomy, and the Blalock operation were studied. A 500-500 proportion of  $C_3H_6 - O_2$  resulted in blood  $O_2$  values between 95% and 100% in patients with normal hemoglobin. These blood levels were usually maintained unless there was a fall in blood pressure.

Seven Blalock operations\* have been studied. Typical data, (Figs. 10 and 11) obtained on a 23-year-old girl who had undergone a Blalock anastomosis, now non-functional, on the left side 18 months prior to the present operation, are shown. She had a left diaphragmatic paralysis. The patient's hemoglobin was 16.1 Gm., since a local physician had subjected her to frequent blood-letting in an attempt to alleviate the polycythemia. Pre-operative medication was morphine sulphate, gr.  $\frac{1}{6}$ , and atropine sulfate, gr.  $\frac{1}{150}$ . The preoperative blood  $O_2$  level was 67% saturated, as proven clinically by a definite cyanosis. The induction with a 500-500  $C_3H_6 - O_2$  mixture, brought the blood  $O_2$  level to 88% saturation within five minutes. This was maintained for about  $\frac{1}{2}$  hour. After the chest was opened the blood  $O_2$  showed a decrease from 83% to 74%. As the blood  $O_2$  level was falling the anesthetist started controlled respiration, which showed a beneficial effect on the  $O_2$  curve within four minutes, after which the blood  $O_2$  level rose steadily to 85% saturated. At the beginning of the second hour the right lung was packed. This created a severe anoxemia, the blood  $O_2$  saturation falling from 85% to 42% saturated within 12 minutes. The blood pressure also fell over this same period from 140/100 to 65/42. The anesthetist switched the patient to 100%  $O_2$  with no apparent improvement, the blood  $O_2$  remaining in the region of 40% saturated for several minutes. During the period not shown in the figures 2 minims of adrenalin were administered intravenously with the result that the blood  $O_2$  rose to 45% for a period of two minutes, after which it dropped back toward 40%. Whole blood was administered, and within the next 45 minutes the blood  $O_2$  saturation rose to 50%. The blood pressure gradually returned to 140/90 during the same period. For the four hours preceding the completion of the anastomosis in the sixth hour of anesthesia the patient's blood  $O_2$  fluctuated between 45% to 50% saturated.

The dramatic increase in blood  $O_2$  is effectively shown by the oxyhemograph at the removal of the clamps after the completion of the end of the subclavian artery to the side of the pulmonary artery anastomosis (Fig. 11). The beneficial effect of inflation of the right lung, of closing the chest and of natural respiration is also recorded. The blood  $O_2$  saturation had reached 89% prior to the removal of the mask. The return to room air is especially

\* To be published.

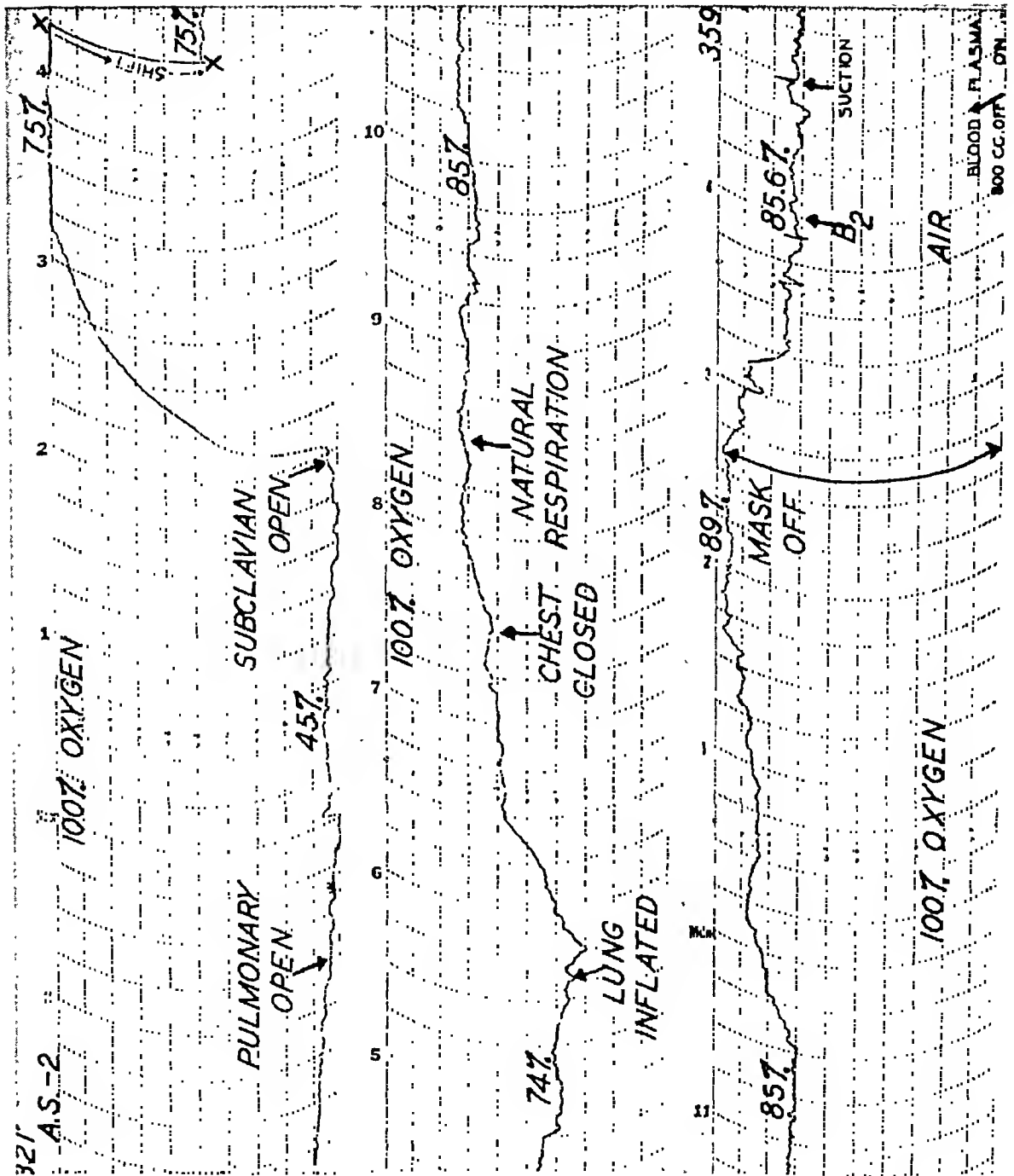


FIG. 11.  
(See Figure 6 for legend.)

CONTINUOUS BLOOD OXYGEN SATURATION ABDOMINAL HYSTERECTOMY

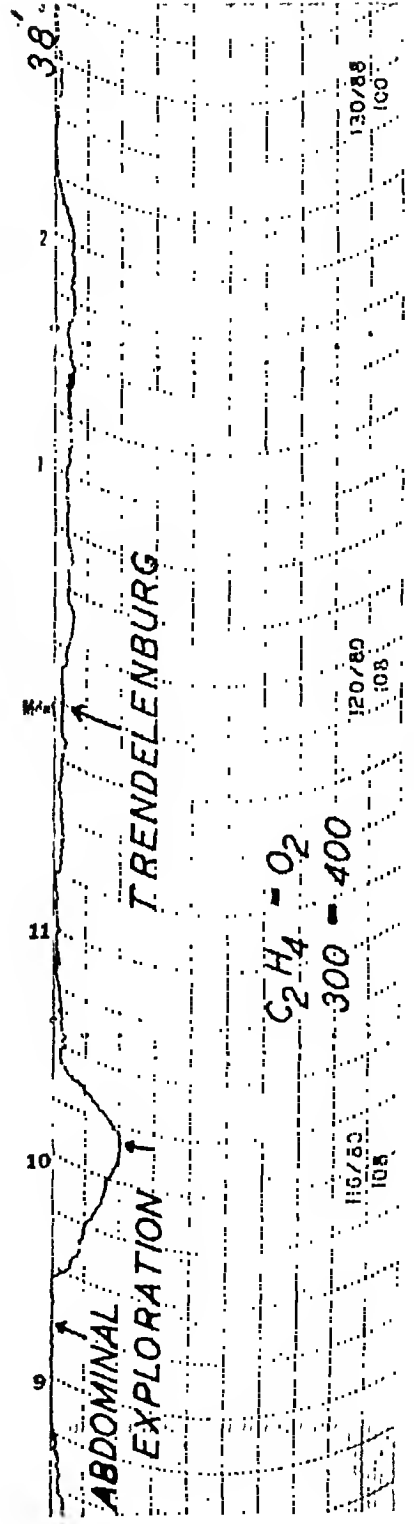
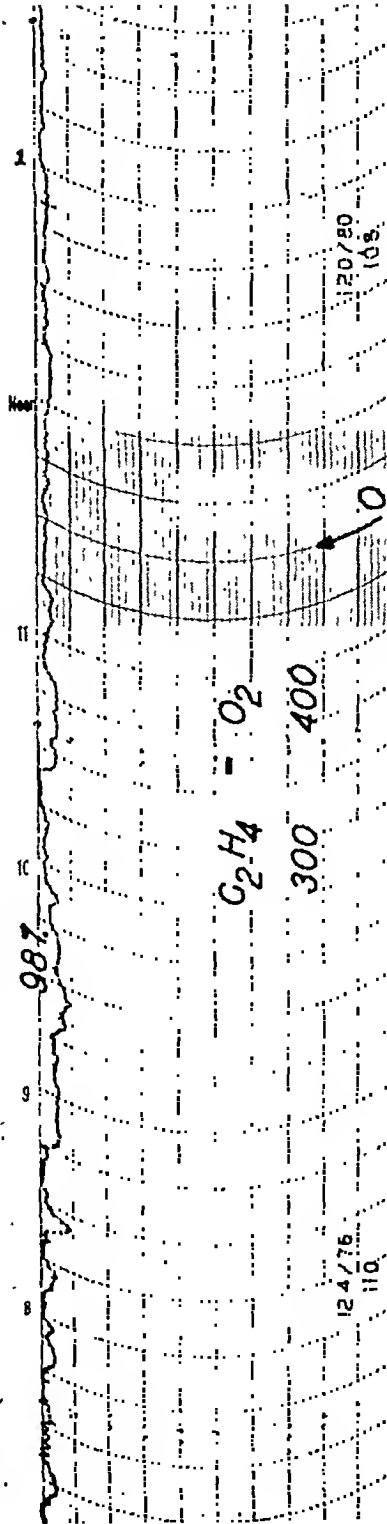
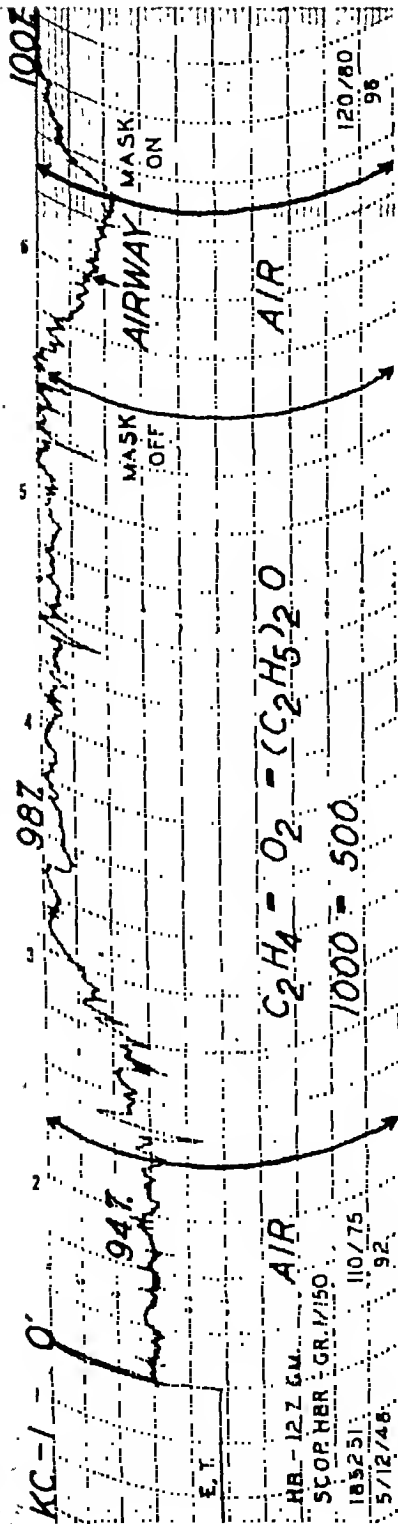


Fig. 12.  
(See Figure 6 for legend.)

significant because it shows a blood  $O_2$  drop of only 4%, in marked contrast to the induction record (Fig. 10). The marked improvement in pulmonary circulation and blood oxygenation effected by the anastomosis is well illustrated.

#### ETHYLENE AND ETHER

Three operations in which  $C_2H_4$  and  $(C_2H_5)_2O$  were administered as the anesthetic have been studied with the oxyhemograph. In each case the blood  $O_2$  was maintained throughout the major share of the operation at normal or above normal values. Two of these operations were complete abdominal hysterectomies, whereas the third was performed for multiple fecal fistulae. The Trendelenburg position, employed in the three cases, created no change in the blood  $O_2$  level at its institution. However, as the horizontal position of the table was restored in 10-15° stages, slight depressions in blood  $O_2$  and blood pressure were noted.

A typical induction on one of the hysterectomies is shown in Figure 12. The blood  $O_2$  saturation rose from 94% in air to 98-100% in the  $C_2H_4$ — $O_2$ — $(C_2H_5)_2O$  mixture. The drop in blood  $O_2$  saturation while the mask was off for the airway insertion is clearly illustrated. The remainder of the chart demonstrates that the blood  $O_2$  saturation remained near 100% except during a manual exploration of the abdomen. The point at which the Trendelenburg position was assumed is also indicated. The effect of returning the patient to the horizontal position, while breathing a 300-400  $C_2H_4$ — $O_2$  mixture is shown (Fig. 13). This was done after 68 minutes of anesthesia as the wound was being closed. The blood  $O_2$  showed an immediate decrease which was alleviated by 100%  $O_2$  inhalation. The blood pressure showed a slight fall during this same period. On breathing room air, the patient's blood  $O_2$  saturation fell to 75%. Further inhalation of  $O_2$  did not alleviate the hypoxemia appreciably. An administration of a 25-75 He —  $O_2$  mixture had no beneficial effect, nor did  $O_2$  under increased pressure. Although the operation was completed within this period, the patient was kept on the operating table about 16 minutes for further observation. Inspiration of room air caused the blood  $O_2$  saturation to fall to 65% whereupon a 100%  $O_2$  inhalation and an intravenous 5% glucose in physiological saline injection (300 cc.) were carried out. The blood  $O_2$  curve reached the low level of 60% saturated, as shown by the tracing, until manual compression of the breathing bag was carried out by the anesthetist for 2 minutes. This forced ventilation seemed to have a beneficial effect because the blood  $O_2$  saturation rose rapidly to 85% and then gradually fell toward 80% as the patient was aroused.

The final stage of another abdominal hysterectomy is shown in Figure 14. The decrease in blood  $O_2$  and in blood pressure created by a 15° rise from the Trendelenburg position is observed. The effect of leveling the table as well as the return to room air created a gradual decrease in blood  $O_2$  saturation from 90% to 56%. While the blood  $O_2$  was decreasing the blood pressure fell from 118/80 to 90/70. When the arterial puncture (blood  $O_2$  —

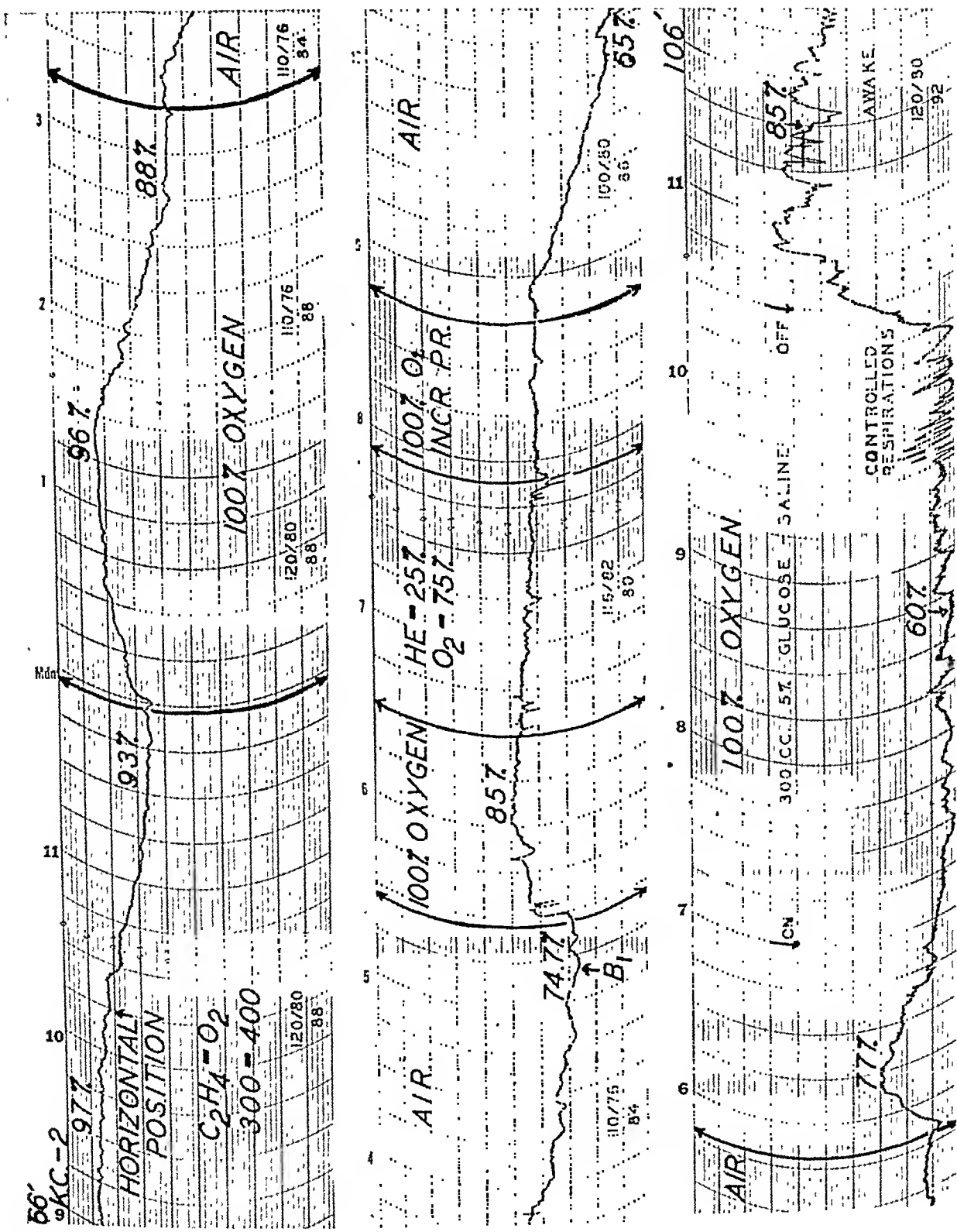
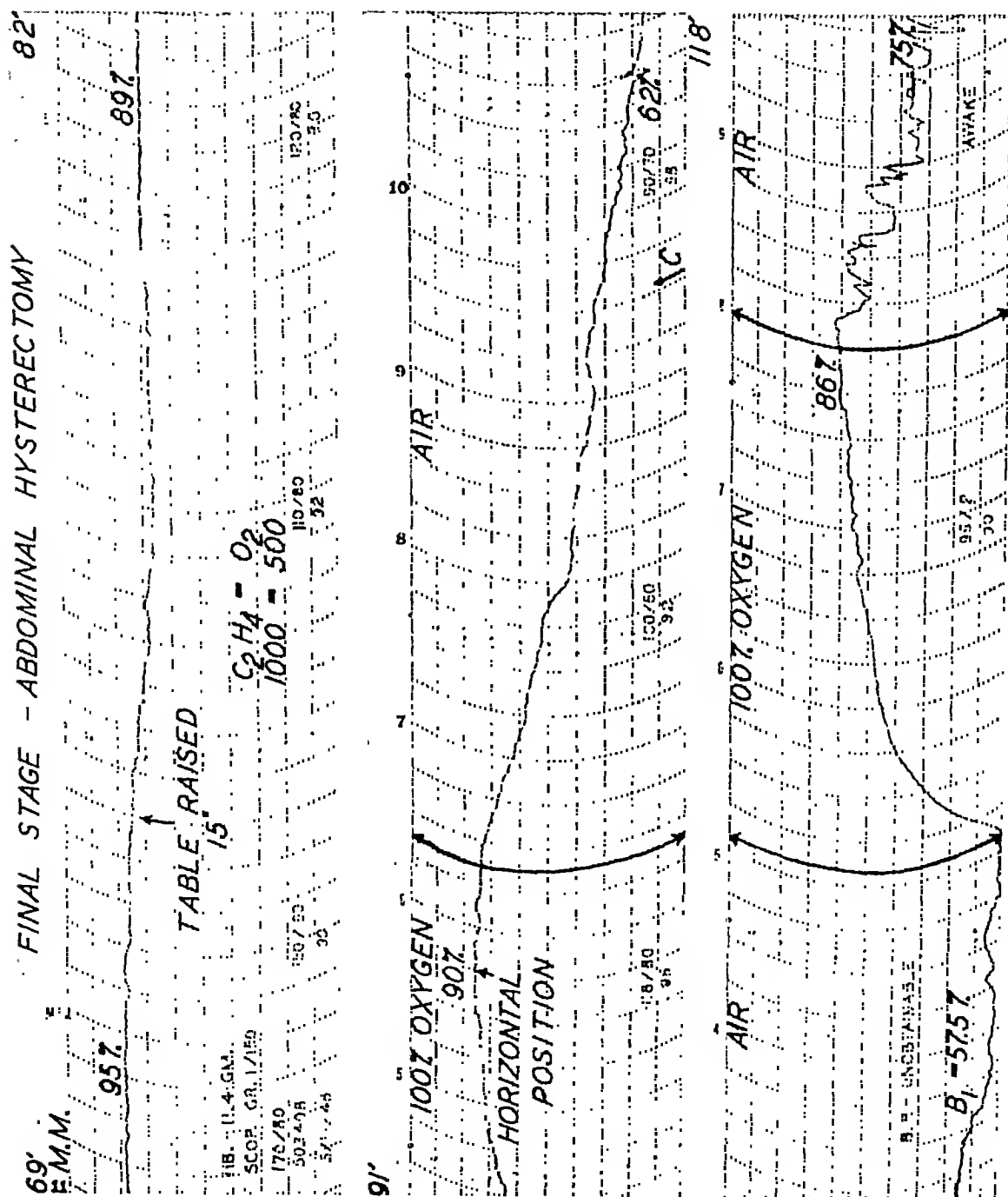


Fig. 13.  
(See Figure 6 for legend.)



57.5% saturated) was done the blood pressure was unobtainable.  $O_2$  inhalation brought the blood  $O_2$  to a level of 86% saturated and the systolic blood pressure to 96 within two minutes. On return to room air the patient showed only a 75% blood  $O_2$  saturation as she awakened.

It is significant that the fall in blood pressure so closely parallels the blood  $O_2$  decrease. The fact that the blood pressure was obtainable after  $O_2$  was administered for two minutes suggests that  $O_2$  lack may be the primary factor. It appears from these few cases that the change from Trendelenburg to horizontal position may play a role in this postoperative hypotension and hypoxemia. Further study of this problem is being carried out at the present time.

#### SPINOCAINE

Four spinocaine anesthetics were observed. In three of these the blood  $O_2$  saturation was maintained within the normal range throughout the operation. In the fourth case, that of a negro undergoing a right inguinal hernia repair, the blood  $O_2$  showed a gradual 25% decrease in saturation. This diminution in blood  $O_2$  occurred as the patient complained of a "heavy" feeling in his chest. A pain sensitivity test proved that the spinal had become effective above the nipple line. Therefore, embarrassment of the respiratory muscles was probably a contributing factor in causing the blood  $O_2$  decrease.

#### SUMMARY AND CONCLUSIONS

1. The importance of determining the oxygen saturation of the blood during anesthesia is emphasized.
2. Blood oxygenation values fluctuate so rapidly and so widely that intermittent gas analysis determinations are inadequate.
3. The portable photoelectric oxyhemograph, which gives a continuous recording of arterial  $O_2$  saturation by means of opposed red and green filtered photoelectric cells, radio amplification (1,000,000 times) and an ink tracing, has supplied reliable and consistent results throughout operative procedures up to 10 hours in duration under various anesthetic agents.
4. Records on patients receiving pentothal show:
  - (a) considerable individual susceptibility.
  - (b) the advantage of 100%  $O_2$  inhalation over room air prior to and during the induction as well as the value of  $O_2$  administration during the course of the anesthesia.
  - (c) the decreasing tolerance to pentothal which prevents adequate blood oxygenation even though 100%  $O_2$  is administered in prolonged procedures.
  - (d) the importance of using at least a 60-40  $N_2O - O_2$  mixture as a supplement to pentothal anesthesia.
  - (e) the necessity for the continuation of  $O_2$  inhalation during the postoperative period, at least until the patient reacts, if anoxemia is to be avoided.
5. Patients receiving cyclopropane, ethylene-ether, a combination of these



or spinocaine as anesthetic agents have not shown decreasing tolerance or cumulative effects as far as could be determined from the oxyhemograph curves.

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DISCUSSION.—DR. ROBERT M. JANES, Toronto: Dr. Behrmann has presented most beautifully what we believe to be a most important subject. At a meeting of the American College of Surgeons in New York last year, my associate, Dr. Kergin, presented some work that we had been doing on this problem. Our attention was

directed to it originally when we found that in doing bilateral resections for bronchiectasis our survivals were not as good after we started to do the dissection instead of the tourniquet operation. The explanation was apparently obvious in that the second operation was much more prolonged. Our studies paralleled very closely those you have heard. Certainly the oxyhemograph seems to give records that correspond sufficiently closely with samples of blood taken from an aorta during operation. We believe many of the unexplained deaths, particularly those in thoracic and abdominothoracic operations, are related to periods of prolonged anoxemia. The clinical estimate is not sufficiently accurate to detect this anoxemia, and we have come to feel that this apparatus should be part of the routine equipment in every operating room where these prolonged and serious operations are being undertaken.

DR. ROY D. McCLURE, Detroit (closing): Oliver Wendell Holmes created a very beautiful word—anesthesia. The word anesthetist soon followed, and now a much more cumbersome, seven-syllable word—anesthesiologist.

We know that anesthesia, with or without preoperative sedation, may produce severe anoxemia or anoxia or, vice versa, severe anoxia may produce some degree of anesthesia.

Ours is a far cry from the first Kramer machine that Hartman worked with 11 years ago, a machine with two photoelectric cells applied to dissected-out artery and vein, two galvanometers each reflecting a beam of light writing on strips of photographic film. We showed this apparatus one sweltering hot summer day to our long-time friend, Charles F. Kettering. Off came his coat and on hands and knees he explored the inside workings of this box. He came up with the statement that the feeble impulses through the photoelectric cells could be amplified in a different way to greatly simplify this process. We developed a one-color photoelectric cell which was attached to the web of the hand of the anesthetized patient in 1939. Today you have seen the result of invaluable improvements, thanks to Kettering.

Milliken, who died so tragically in the mountains of Tennessee last spring, further developed this principle so that a photoelectric cell could be placed on the ear of an aviator inside his helmet, and when the oxygen content of his blood decreased at high altitudes a red light would flash on the instrument panel of his plane.

We believe that this method is developing into great practical value in our operating rooms. A number of cases have been reported of patients, blue under anesthesia, who became "vegetables" (not for dining-table use, however) as a result of cerebral anoxia. There are undoubtedly many who suffer some permanent mental deficiency after anoxia without the cause ever being recognized. I would like to cite one case of many that have come to my personal attention. A brilliant girl student at Ann Arbor returned for a weekend with her parents in Detroit, and had her dentist extract an impacted molar tooth under nitrous oxide anesthesia. Shortly afterward she noticed slight double vision, but paid little attention to it. On returning to college she lacked concentration, her grades became poor and she finally flunked out. In my own mind there is no doubt that this was the result of anoxia. At the end of the year she returned to the same dentist for extraction of the opposite molar and was told by him—"Never take nitrous oxide for you can't stand it. Last year you got blue, stopped breathing, and we had to give you artificial respiration."

Perhaps routine mental tests in the early days of anesthesia, before and after prolonged or even short anesthesia, would have revealed many such cases. Our previous work has emphasized the dangers of oversedation with barbiturates and with morphine.

Dr. Hartman and Dr. Behrmann had hoped to show on our slides today simultaneously with these curves the continuous recording of the blood pressure, but this will soon be published.

# PENICILLIN THERAPY WITH PROLONGED INTERVAL DOSAGE SCHEDULES\*

W. A. ALTEMEIER, M.D.

CINCINNATI, O.

THE DOSAGE SCHEDULES devised for the therapy with penicillin of susceptible surgical infections have been based upon the assumed necessity of maintaining a therapeutic concentration of this agent in the circulating blood and tissues. This assumption probably resulted from a transfer of previous experiences with the sulfonamides. The effectiveness of dosage schedules based upon this concept has been established without question,<sup>1-4</sup> but each method has had one or more objections which have made it undesirable. The continuous infusion of penicillin either intravenously or intramuscularly, was soon abandoned in favor of single injections at intervals of two to four hours because of the patient's discomfort and the amount of time and effort needed to insure its efficiency. In this way the rapid excretion of penicillin was offset by the injection of penicillin at short intervals, but the inconvenience to patient and physician and the impossibility of administering penicillin to anyone but a hospitalized patient stimulated a further search for more satisfactory methods. Three plans were devised to overcome these objections and to extend the usefulness of penicillin to ambulatory or unhospitalized patients: delayed absorption, delayed excretion, and oral administration.

Delayed absorption, with the maintenance of a prolonged level in the blood, has been accomplished in several ways. With preparations of penicillin in oil and beeswax<sup>5</sup> or suspensions of penicillin in oil and pectin,<sup>6</sup> the absorption of water soluble penicillin was delayed by beeswax or pectin. An effective blood level for 24 or more hours can be maintained in 70 to 80 per cent of the cases with daily injections of 300,000 units in oil and if the dose is increased to 400,000 units, the level will be satisfactory in almost all of the cases for 24 or more hours. It has also been possible to retard the absorption by the injection of insoluble salts of penicillin. Our preference among these at the moment is procaine penicillin<sup>7</sup> prepared for parenteral injection either in an oil base or aqueous solution. Both have certain advantages over the oil and beeswax preparations, including a lower incidence of pain and local reaction. Other salts of penicillin with a low water solubility and slow rate of absorption are those formed by the heavy metals such as bismuth, silver, and mercury.

Retarded excretion of penicillin has been produced by the oral administration of caronamide in doses of 3 Gm. every four hours for periods of 2 to 19 days.<sup>9, 10</sup> This may be used to either decrease the interval between injections of aqueous penicillin, to enhance the blood levels two to seven times, or to decrease the amount of penicillin necessary for therapy of a given case. Two of its disadvantages are the large daily doses required and the nausea produced in some instances.

The oral administration of penicillin has been used effectively in selected cases providing it was buffered and its dose was five times greater than that of the necessary parenteral dose.<sup>3</sup> The ingestion of 100,000 units of buffered

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\* Read before the American Surgical Association, Quebec, Canada, May 28, 1948.

penicillin at intervals of four to six hours can usually be depended upon to produce and maintain a satisfactory concentration in the blood, and in its scope of application, it has been particularly useful in the therapy of ambulatory patients.

TABLE I.—*Clinical Results with Eight-Hour Penicillin Dosage Schedule*

Diagnosis	No. of Cases	Surgery	Results			
			Excellent	Good	Quest.	Failure
I. Staphylococcal Infections						
Cellulitis .....	20	4	13	7	..	..
Abscess .....	17	16	5	11	1	..
Infected wounds .....	15	4	5	9	1	..
Ulcer with cellulitis.....	5	..	5	3	1	..
Acute mastitis .....	3	..	..	1	2	..
Furunculosis .....	2	..	2	2	..	..
Parotitis .....	2	..	..	..	..	..
Carbuncle .....	2	..	2	2	..	..
Subacute osteomyelitis .....	2	..	..	2	..	..
Hydradenitis .....	1	..	1	..	..	..
II. Streptococcal Infections						
Cellulitis .....	8	1	6	1	1	..
Abscess .....	4	3	2	2	..	..
Infected wounds .....	4	..	2	1	..	1
Lymphangitis .....	2	..	2	..	..	..
Septicemia .....	2	..	1	..	..	1
III. Mixed Staphylococcal and Streptococcal Infections						
Ulceration and cellulitis.....	9	4	1	5	2	..
Abscess .....	9	6	3	7	..	..
Infected wounds .....	9	3	2	6	1	..
Cellulitis .....	4	2	2	..	2	..
Lymphangitis .....	2	..	2	..	..	..
Pleural empyema .....	2	2	..	2	..	..
IV. Pneumococcal Infections						
Postoperative pneumonia .....	6	..	3	2	1	..
Septicemia .....	1	..	1	..	..	..
V. Mixed Infections						
Peritonitis .....	12	12	..	5	6	1
PO wound infections.....	4	2	3	..	1	..
Acute cholecystitis .....	4	4	..	2	2	..
Deep abscess of neck.....	3	3	2	1	..	..
Intra-abdominal abscess .....	3	2	..	..	3	..
Acute salpingitis .....	3	1	..	2	1	..

It is well established, therefore, that the administration of adequate amounts of penicillin by any dosage schedule which maintains a more or less constant concentration of the agent in the blood will produce efficient chemotherapy. However, the necessity of maintaining a therapeutic concentration in the blood for successful treatment has not been proved, and evidence is accumulating that the bacteriostatic effect of penicillin persists for a considerable length of time after its disappearance from the blood. As early as 1944, the results of Tillet, et al,<sup>11</sup> suggested that penicillin inhibited the growth of invasive pneumococci for a considerable period after blood concentrations were no longer measurable. When injections were made at intervals of 12 to 16 hours, the results seemed to be just as satisfactory as those obtained when more frequent injections were used to maintain a therapeutic concentration throughout. Similar inhibitory effects on streptococci infecting mice for eight or more hours were suggested by the studies of Jawetz<sup>12</sup> in 1946. The studies of Zubrod<sup>13</sup> also indicated that the interval between doses on an aqueous solution of peni-

cillin could be greatly increased beyond four hours in the management of hemolytic Streptococcic infections in mice. More recently Marshall,<sup>14</sup> after discussing the discrepancies in methods of chemotherapy with penicillin and indicating his belief that the maintenance of a more or less constant blood concentration was unnecessary for efficient treatment in the human, advocated

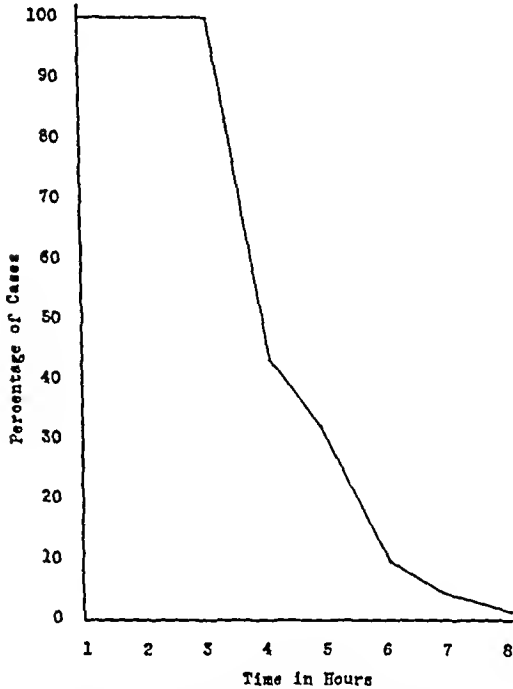


FIG. 1.—Showing the percentage of cases maintaining a concentration of .03 units of penicillin or more per c.c. of plasma 1 to 8 hours after a single intramuscular injection of 100,000 units of penicillin in aqueous solution.

carefully controlled clinical trials to evaluate the efficiency of three, two, or even one injection per day in human infections. Preliminary studies of this nature at the Cincinnati General Hospital were reported shortly thereafter.<sup>15, 16</sup>

#### MATERIAL AND METHODS

The current acute shortage of nursing personnel has stimulated us to explore the clinical effectiveness of the simple injection intramuscularly of larger doses of penicillin in aqueous solution every 8 to 12 hours. During the past eight months, we have treated 161 selected cases of established surgical infections at the Cincinnati General and neighboring hospitals. Externally located infections of moderate severity and known etiology were chosen for study in the majority of instances and most of them were produced by the hemolytic

*Staphylococcus aureus* and/or the hemolytic Streptococcus. (Table I.)

Each of the cases was treated with either 100,000 units of penicillin at intervals of eight hours or 150,000-200,000 units at intervals of 12 hours. The penicillin was dissolved in sterile physiologic saline and injected intramuscularly using a volume of 1 cc. per 100,000 units. Determinations of the blood levels were made at intervals of one hour in 68 of the patients to determine the concentration of penicillin produced by one intramuscular injection. Whenever possible, the infecting bacteria were identified at the start of penicillin therapy and their susceptibility to penicillin determined in vitro. Studies were also made to determine the degree and duration of any inhibitory effect of a single application of two units of penicillin per cc. on the growth in vitro of five strains of the hemolytic *Staphylococcus aureus*, the hemolytic Streptococcus, the non-hemolytic *Staphylococcus*, and the non-hemolytic Streptococcus.

#### RESULTS

*Measurements of Penicillin in the Blood.* Considerable variation in the levels produced by a single intramuscular injection of 100,000 units of penicillin

was obtained in 68 cases. Concentrations in excess of .03 units per cc. were maintained for at least three hours in 100 per cent of the cases, for four hours in 43 per cent, for 5 hours in 31 per cent, for six hours in 7 per cent, and for seven hours in 4 per cent. (Fig. 1.) Thus, an adequate level of penicillin was maintained through the eight hours in only 1.4 per cent of the cases. The two extremes of variation encountered in the levels of penicillin produced by a single injection of 100,000 units intramuscularly are illustrated in Figure 2.

*Lag in Bacterial Growth Following Temporary Exposure to Penicillin.*  
When five strains of the hemolytic *Staphylococcus aureus* which had been isolated from established human infections were exposed for two to four hours

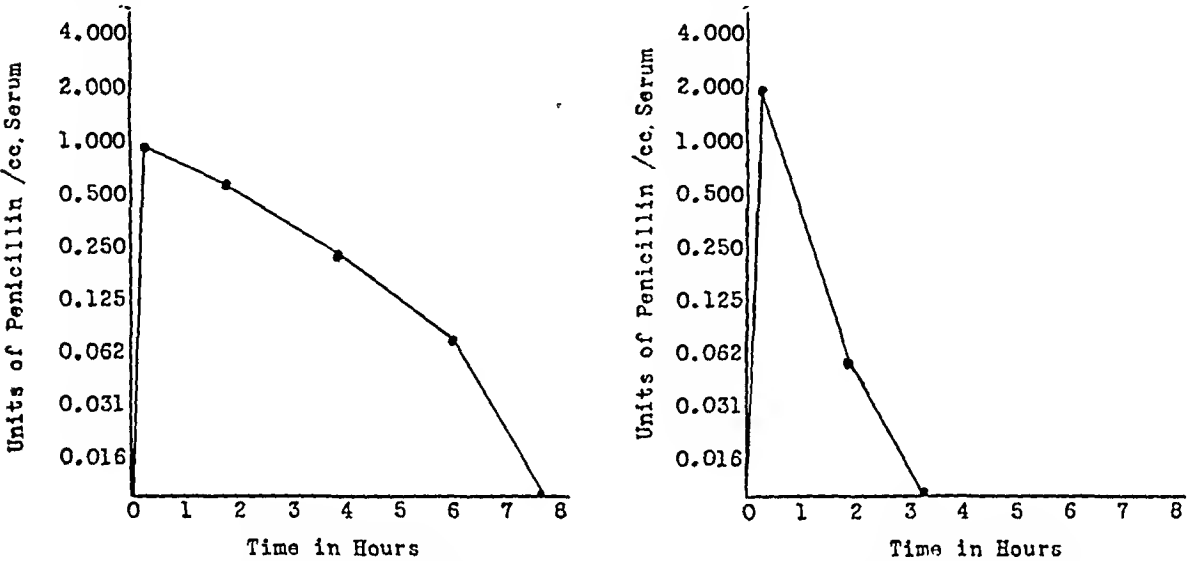


FIG. 2.—Illustrating the variation in blood levels obtained following a single injection of 100,000 units of penicillin in aqueous solution intramuscularly.

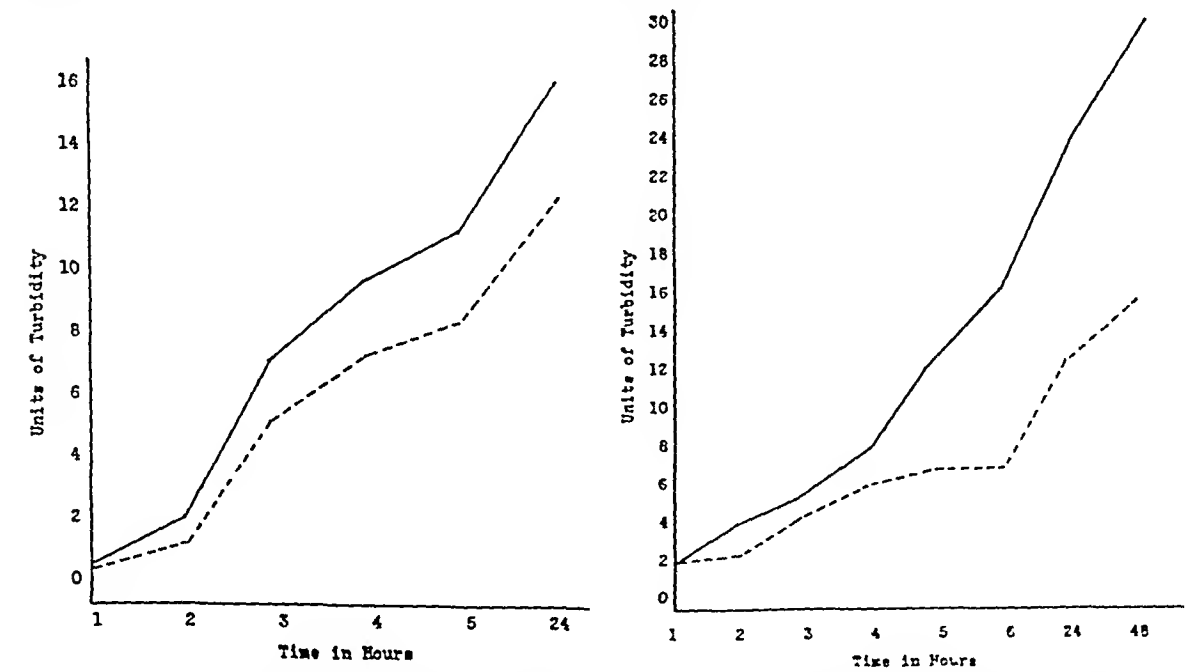


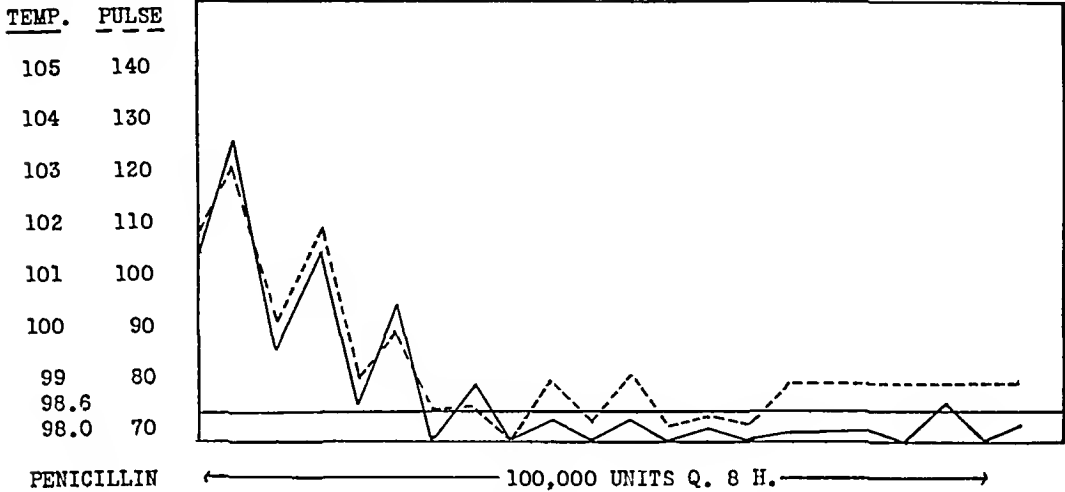
FIG. 3.—Illustrating the lag in growth of hemolytic *Staphylococcus aureus* produced by 2 hour exposure to 2 units of penicillin per c.c.  
—— No exposure to penicillin  
----- Two hour exposure to penicillin

FIG. 4.—Illustrating the lag in growth of the hemolytic *Streptococcus* following a 4 hour exposure to 2 units of penicillin per c.c.  
—— No exposure to penicillin  
----- Four hour exposure to penicillin

to the effect of two units of penicillin per cc. of media, a definite lag in their growth persisted for 8 to 24 hours after penicillin was removed and the organism reinoculated into fresh media without the chemotherapeutic agent. (Fig. 3.) Similar but less striking results were obtained with strains of the hemolytic

DATE OF ADMISSION: 12-1-47

DAY OF ILL.: 3 4 5 6 7 8 9 10 11 12 13

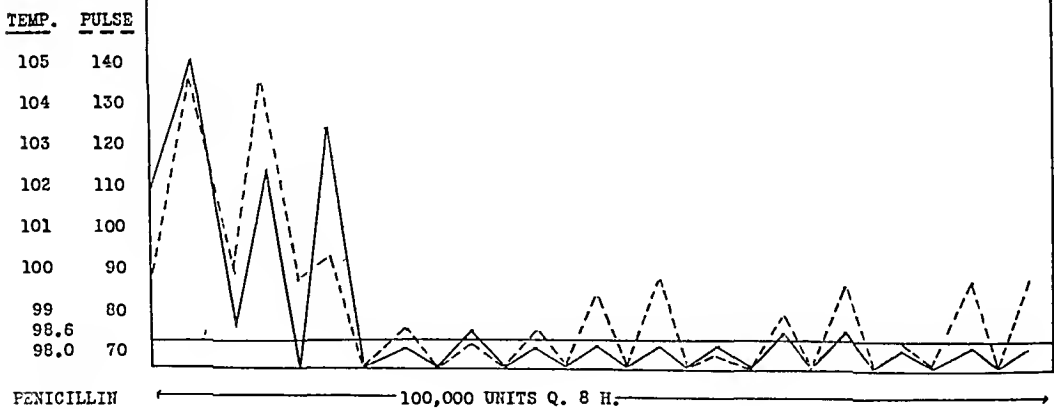


W. B. C. 27.5 27.1 22.7 18.45 13.95 9.1 9.5

FIG. 5.—G. S. Infected laceration of right arm with cellulitis, lymphangitis, and lymphadenitis in a 38 year old colored female.

DATE OF ADMISSION: 1-22-48

DATE OF ILL.: 2 3 4 5 6 7 8 9 10 11 12 13 14 15



W. B. C. 33.5 18.5

FIG. 6.—B. H. Age 25. Excellent response with complete control and spontaneous resolution of an acute interstitial mastitis of left breast following chemotherapy with 100,000 units of penicillin every 8 hours.

Streptococcus (Fig. 4), the non-hemolytic Streptococcus, and the non-hemolytic Staphylococcus.

*Clinical Results.* The clinical results obtained in this series of selected cases were very gratifying and probably indistinguishable from those anticipated with the three or four hourly injections of penicillin with two possible exceptions of severe and extensive infections caused by the hemolytic Streptococcus in which penicillin therapy first with 100,000 units every eight hours

and later every three hours failed to save the patient's life. An arbitrary classification of the clinical results obtained with this dosage schedule is given in Table I. A satisfactory result was obtained in the great majority of the Staphylococcal infections treated and the pattern of response was the same

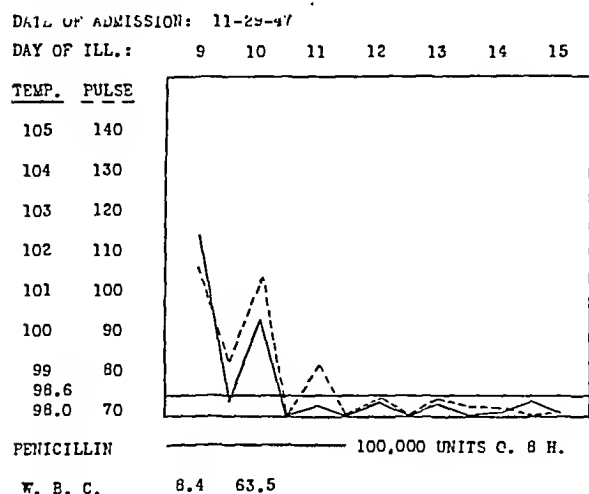


FIG. 7.—J. K. Age 14. Post traumatic ulcer of the leg with extensive cellulitis and lymphangitis produced by a hemolytic Streptococcus.

which we have learned to expect with a lag of 24-72 hours preceding any obvious clinical change, spontaneous resolution of the earlier cases, and control of the invasive characteristics and localization in the later cases. (Figures 5, 6.) The Streptococcal infections were generally more severe than the other types, but satisfactory chemotherapeutic results were obtained in 17 of the 20 cases. The two failures occurred in fulminating and extensive infections produced by the hemolytic Streptococcus. In the

mixed infections produced by both gram positive and gram negative bacteria, the incidence of satisfactory results was only 50 per cent as could be anticipated.

*Serial Measurements of Bacterial Sensitivity.* In only one case was evidence detected of a susceptible hemolytic *Staphylococcus aureus* developing definite resistance to penicillin during therapy with this schedule.

#### DISCUSSION

Experimental and clinical evidence indicates that the antibacterial effect of penicillin persists for some unknown reason for a considerable length of time after its disappearance from the circulating blood. Although this is a relatively small series of cases from which to draw any conclusions, it appears that the maintenance of a more or less constant blood level is probably unnecessary for efficient therapy in the human being. In our limited clinical experience, it appears that the intramuscular injection of an aqueous solution of penicillin containing 100,000-200,000 units every eight to 12 hours is an efficient and effective method of chemotherapy in susceptible infections of moderate severity. The method overcomes the disadvantages and inconveniences of the two- to four-hour dosage schedule to a large extent and has not resulted in any increased tendency of the bacteria to develop resistance of penicillin. The administration of only two or three injections per 24 hours decreases the task of the nurse and releases part of her time for other more necessary nursing duties.

In addition to the lessened discomfort and inconvenience of the patient, the method is of great practical importance at the moment because of the nursing shortage throughout the nation. The eight- and 12-hour dosage schedule is advocated at present only in susceptible infections of moderate severity or less until further experimental information is gathered.



# THE RESULTS OF THE SYSTEMIC ADMINISTRATION OF THE ANTIOBIOTIC, BACITRACIN, IN SURGICAL INFECTIONS. A PRELIMINARY REPORT\*

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BACITRACIN IS AN ANTIBIOTIC produced by the Tracey strain of *Bacillus subtilis*. It was isolated from the mixture of organisms found in the debrided tissues removed from a compound fracture of the tibia, while studying the prevention of infection in contaminated wounds by the use of sulfonamides.<sup>1</sup> Its commercial production has met with some difficulties similar to those encountered during the development of both penicillin and streptomycin.

During the early stages of the process of purification, bacitracin was used in the local treatment of various types of surgical infections and the first 100 cases were reported in March, 1947.<sup>2</sup> It yielded favorable results comparable to penicillin, and in many cases in which penicillin had failed. It was then taken up by the dermatologists, Miller and Slatkin, who reported success in the treatment of various types of pyoderms.<sup>3</sup> Similar encouraging reports were made in the field of ophthalmologic infections.<sup>4</sup>

During the past 20 months, purification and standardization have reached a point which has permitted the systematic use of bacitracin. A number of groups are trying to evaluate this antibiotic in the systemic treatment of pneumonia, syphilis and various types of surgical infections. These studies are being carried out with the aid of funds provided by the Medical Research and Development Board of the Surgeon General's Office and the Antibiotics Study Section of the National Institute of Health. The leaders of these groups are co-authors in the presentation of this report.

The Surgeon General's Office called upon the Food and Drug Administration to set up specifications and tentative standards for bacitracin which would permit its systemic use under experimental conditions and which would safeguard the patients during the course of its clinical appraisal. Therefore, on January 20th of this year, Dr. Henry Welch called the manufacturers together and they subsequently agreed upon provisional specifications regarding potency, solubility, stability, toxicity for mice, pyrogenic effects for rabbits, and vasopressor and vasodepressor effects on dogs. These minimum specifications must be met by all of the manufactured preparations before they can be applied in the treatment of human infections.

Bacitracin has a wide antibacterial spectrum, being effective against most strains of hemolytic streptococci, nonhemolytic streptococci, coagulase-

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\* Read before the American Surgical Association in Quebec, Canada, May 28, 1948.

positive staphylococci, pneumococci, gonococci, anerobic cocci in general, all of the gas gangrene group of organisms and the bacillus of tetanus, the diphtheria bacillus and diphtheroids, the spirochetes of syphilis and mouth spirochetes, the actinomycotic group of organisms, and among the protozoans, the *Endamoeba histolytica*. There is little or no action against the large group of aerobic Gram negative non-spore forming bacilli.

The chief advantages that bacitracin has over penicillin are (1) that it is not inhibited by the organisms which produce penicillinase and is, therefore, more likely to be effective in infections due to bacterial mixtures. (2) It is more slowly eliminated from the body and, therefore, can be given at longer intervals. (3) Its effectiveness against bacteria is in direct proportion to its concentration.<sup>5</sup> This has been brought out by Eagle in comparing the lethal action of penicillin and bacitracin against the spirochetes of syphilis. He has also demonstrated a significant synergistic action between penicillin and bacitracin in the treatment of experimental syphilis whereby small fractions of therapeutic doses of each, when combined, yield a therapeutic result.<sup>6</sup> (4) So far, bacitracin has shown less tendency to produce allergic or hypersensitive reactions but these may come with its more extended use. Certain strains of bacteria gradually build up a resistance to bacitracin but this is of a low order. As time goes on, more and more organisms belonging to groups susceptible to penicillin are proving to be resistant to it and in many instances these organisms are susceptible to bacitracin.

Its chief disadvantage, as compared with penicillin, is that it has not yet been obtained in a pure or crystalline form and, in the present state of its impurity, it produces, when injected systemically in man, certain evidence of nephrotoxicity which limits its dosage and the duration of treatment. This will be discussed more fully below.

Its chief advantages over streptomycin are its wider antibacterial spectrum, particularly with regard to the anaerobic organisms, and the low order of the development of resistance during the course of treatment. Its chief disadvantage with respect to streptomycin is its ineffectiveness against the Gram negative aerobic non-spore forming bacilli.

While bacitracin is not inactivated by gastric acidity or by the proteolytic ferments of the gastro-intestinal tract, it is not absorbed to any extent from the alimentary canal. However, while it cannot be given systemically as a mouth medication, it remains active and effective against the susceptible groups of intestinal organisms, particularly the *Clostridium welchii* and the intestinal streptococci, and it can be recovered from the feces in a concentration well above the lethal level for these organisms. It may, therefore, be combined with streptomycin or some of the relatively insoluble sulfonamides to minimize the activity of the intestinal flora before surgical procedures on the bowel. It has also been found effective in a few cases of intestinal infections, namely, in chronic ulcerative colitis

and regional ileitis. Furthermore, encouraging results are being obtained by mouth administration in both the acute and chronic stages of amebic dysentery.

The present report includes 105 cases of surgical infections observed in the units set up for the appraisal of bacitracin in New York, Cincinnati, New Orleans, San Antonio and Philadelphia. These studies are being carried on in a uniform manner and comparable data are being obtained in all cases. These data are being recorded on summary sheets especially prepared for this study, designed to bring out the essential features of these cases. In the course of the coming year, it is hoped that records will be obtained on approximately 1000 cases. Plans are going forward to analyze the results and determine their statistical significance so that at the end of that time, we may have a clearly defined knowledge of the indications for and limitations of this new antibiotic. These data will be collected and analyzed at the unit in New York.

The information which is being gathered with regard to various types of surgical infections includes diagnosis and duration (30 days having been set as the dividing line between acute and chronic infections); a record of the previous treatment, if any, both local and systemic; the general status of the patient as indicated by the blood count, sedimentation rate and kidney function, including the tests for nonprotein nitrogen or blood urea nitrogen, the clearance of phenolsulfonephthalein, and the presence of albumin, sugar, casts and cellular elements; the dosage of bacitracin, both systemic and local; the symptoms and signs of infection before and during treatment; the time relationship of any surgical procedure; the blood levels; the per cent of bacitracin excreted in the urine; a complete bacteriologic analysis of the infection before, during and after treatment and the results obtained.

It is understandable, since the advent of the sulfonamides and the antibiotics, particularly with the ready availability of penicillin and its low toxicity, that patients coming to any hospital with an infection are likely to have had some form of antibacterial therapy either self-administered or prescribed by the family doctor. This means that today relatively few patients are available for primary treatment with a new form of therapy. This is a handicap to the success of the new agent because it not only increases the proportion of cases which are resistant to all treatment but prolongs the duration of the illness before the institution of the new form of treatment. Until confidence can be built up in a new drug, doctors are not warranted in using it in the primary treatment of an infection. In view of these facts, the authors of this paper recognize that bacitracin will not be of any practical importance unless it can succeed where other forms of treatment have failed or unless it can demonstrate its clear-cut superiority over other forms of treatment so that it becomes the treatment of choice. As time goes on, however, if bacitracin demonstrates its effectiveness and

its safety and if the cases in which it is used are carefully studied and the indications for and the limitations of this treatment can be clearly defined, then it may be that certain conditions will indicate its use as the initial treatment.

During the preliminary stages of this investigation, the leaders of each group have proceeded cautiously with relatively small doses and a large proportion of the cases herewith reported include those which have failed to respond to other forms of treatment. Any statistical analysis of the results of such treatment must keep this in mind. It is exceedingly difficult to run parallel series of cases and to compare different forms of treatment with one another and, in any study of established infections, the controls must lie in the cases themselves and their response to previous forms of treatment.

Bacitracin has been used systemically in steadily increasing number of cases for the past year and a half. This number has been limited chiefly by production difficulties in obtaining a uniform product of consistent potency and low toxicity. More than 100 cases of syphilis have been treated by Eagle and his associates with bacitracin or a combination of bacitracin and penicillin. Reisner has treated over 25 cases of pneumonia. These will be reported elsewhere. A few other so called medical infections, such as malignant endocarditis, have been treated and others are being studied. This paper covers all of the cases of surgical infections so far treated systemically in the units set up especially for the appraisal of bacitracin and comprises 105 cases, the results of which are shown in the accompanying Table I.

TABLE I.—Results Obtained in 105 Cases of Surgical Infections Treated by the Systemic Administration of Bacitracin

DIAGNOSIS	RESULTS OF TREATMENT				
	Total Cases	Excellent	Good	Case-sterile	No Effect
Cellulitis .....	1	1	0	0	0
Deep abscess .....	1	1	0	0	0
Infected accidental wound .....	1	1	0	0	0
Chronic osteomyelitis .....	1	1	0	0	0
Operative wound infection .....	1	1	0	0	0
Multiple furuncles .....	1	1	0	0	0
Synergistic gangrene .....	1	1	0	0	0
Simple ulcer of skin .....	1	1	0	0	0
Ulcerative colitis .....	1	1	0	0	0
Thrombophlebitis .....	1	1	0	0	0
Brain abscess .....	1	1	0	0	0
Acute osteomyelitis .....	1	1	0	0	0
Undermining burrowing ulcer .....	1	1	0	0	0
Amphicarpous .....	1	1	0	0	0
Infected compound fracture .....	1	1	0	0	0
Meningitis .....	1	1	0	0	0
Human bite infection .....	1	1	0	0	0
Regional ileitis .....	1	1	0	0	0
Carbuncle .....	1	1	0	0	0
Miscellaneous* .....	1	1	0	0	0
TOTALS .....	105	92	80	75	13

Favorable results in 69% of cases.

\* Includes one case each of septic abortion, breast abscess, caliculi abscess, dental abscess, mediastinitis, acute suppurative tonsillitis, bronchitis, cholangitis, ulcerations of glands of neck, strangulated hernia, pelvic thrombophlebitis, intestinal obstruction, ulcers of perineum and scrotum, tetanus with gangrene of foot.

and regional ileitis. Furthermore, encouraging results are being obtained by mouth administration in both the acute and chronic stages of amebic dysentery.

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TABLE I.—Results Obtained in 105 Cases of Surgical Infections Treated by the Systemic Administration of Bacitracin

DIAGNOSIS	RESULTS OF TREATMENT				
	Total Cases	Excellent	Good	Questionable	No Effect
Cellulitis .....	17	6	9	0	2
Deep abscess .....	15	0	10	2	3
Infected accidental wound .....	13	6	4	1	2
Chronic osteomyelitis .....	7	0	6	1	0
Operative wound infection .....	4	1	1	1	1
Multiple furuncles .....	4	0	2	1	1
Synergistic gangrene .....	3	3	0	0	0
Simple ulcer of skin .....	3	0	2	1	0
Ulcerative colitis .....	3	0	2	1	0
Thrombophlebitis .....	3	0	0	3	0
Brain abscess .....	3	0	0	0	3
Acute osteomyelitis .....	2	0	1	0	1
Undermining burrowing ulcer .....	2	0	2	0	0
Actinomycosis .....	2	0	1	1	0
Infected compound fracture .....	2	0	1	0	1
Meningitis .....	2	2	0	0	0
Human bite infection .....	2	2	0	0	0
Regional ileitis .....	2	0	2	0	0
Carbuncle .....	2	0	2	0	0
Miscellaneous* .....	14	2	5	3	4
TOTALS .....	105	22	50	15	18

Favorable results in 69% of cases.

\* Includes one case each of septic abortion, breast abscess, calcified abscess, decubital ulcer, mediastinitis, acute suppurative tenosynovitis, bronchiectasis, cholangitis, tuberculosis of glands of neck, strangulated hernia, pelvic thrombophlebitis, intestinal obstruction, ulcers of perineum and scrotum, tetanus with gangrene of foot.

The results of treatment are classified into four groups. They are called 'Excellent' if infection subsided rapidly and dramatically within 72 hours. They are called 'Good' if there was a definite response to the drug but the effect was more gradual during the course of a week or ten days. The benefit is 'Questionable' if the case might have done just as well without the drug, and the result is labeled 'No Effect' if the infection went on its course regardless of drug treatment.

The results which are called either 'Excellent' or 'Good' may be considered together as favorable results and the other two categories as unfavorable results, although, in the 'Questionable' group, there may be some cases in which the drug was of value. However, in order not to seem too optimistic, the doubtful cases are not put to the credit of bacitracin.

It will be seen that only three diagnostic groups include more than ten cases and the results in the smaller groups are not of statistical significance nor necessarily representative of what might be expected in those conditions. If we take the group as a whole, we find that the results were favorable in 69 per cent of the cases, whereas in the three categories having the largest number and almost one-half of the cases the results were favorable in 78 per cent. In the miscellaneous group including one case of each diagnosis, favorable results were obtained in only 50 per cent of the cases.

It is of interest that in three groups all of the results were 'Excellent,' namely, synergistic gangrene, meningitis, and human bite infection. These meningitis cases were associated with surgical conditions and, while this disease is not ordinarily considered a surgical infection, they are included in this report. It has been found that bacitracin does not penetrate well into the spinal fluid, only reaching a tenth of the level found in the blood<sup>7</sup> but in the presence of infection this penetration is increased.<sup>8</sup> However, if local application can be made by intrathecal injection or topical application, it is effective against susceptible organisms if it can reach the area involved, and it is not locally injurious to the meninges. In the cases of synergistic gangrene, these results are particularly significant because in every case this painful destructive process had spread over a large area of the body surface over a period of months, unchecked by many different forms of treatment including the sulfonamides and penicillin and in each instance the process came to a sudden halt within 72 hours, the necrotic skin was automatically loosened and subsequently separated from the necrobiotic zone, and the areas became covered with epithelium spontaneously without the necessity for any surgical procedure, even skin grafting. It will be remembered that this rare but distressing condition formerly required wide excision in order to effect a cure. Human bite infections may be particularly amenable to bacitracin therapy if given before extensive destruction of tissue has occurred because of the striking susceptibility of anaerobic streptococci and spirochetes.

The highest percentage of favorable results, 88 per cent, was obtained in the cases of cellulitis. This might be expected because organisms causing

these diffuse lesions are usually susceptible to bacitracin and because patent blood vessels permit the infiltration of any medication into the zone of infection. Furthermore the alarming nature of such a case often brings the patient to the doctor in the early stages of the disease.

It is perhaps of equal interest from a scientific point of view to point out those two groups in which the results were unfavorable, namely, throm-



FIG. 1.

FIG. 1.—Patient O.S.: Cellulitis of arm of four months' duration with seven sinus openings, two incisional and five spontaneous, before bacitracin treatment.



FIG. 2.

FIG. 2.—Patient O.C.: One month after bacitracin treatment. Sinuses all healed and surgery obviated.

bophlebitis and brain abscess. In the former group, the element of infection is probably secondary to physical and chemical changes in the blood, while in the cases of brain abscess there are other factors prejudicial to success which will be discussed later.

Although they were few in number, the encouraging results obtained in ulcerative colitis and regional ileitis suggest a thorough investigation of the value of bacitracin in these fields because of the fact that it may be administered by mouth for its local action on the bowel as well as systemically by muscular injection. Like streptomycin, as we have mentioned above, bacitracin is not absorbed to any extent from the alimentary tract, and comes through in the stool in a concentration well above the lethal level for susceptible organisms such as the streptococci and clostridia. Although the



causes of these diseases are not known, infection is of major importance and may be either primary or secondary.

In studying the results obtained in these cases, it seems to the authors to be particularly worthwhile to analyze the two extremes, namely, those yielding prompt, dramatic, almost immediate response to the drug treatment and those in which there is patently or obviously no effect whatsoever. In the



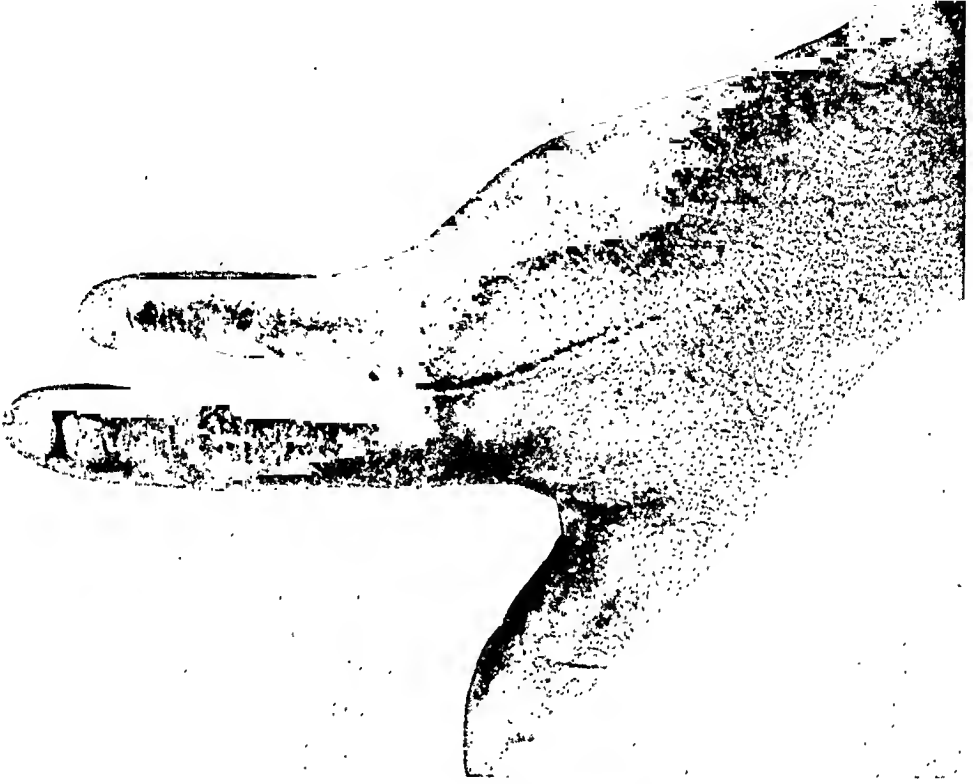
FIG. 3.—Patient E.W.: Actinomycosis of hand eleven months after human bite, before bacitracin treatment

'Excellent' group, there are 22 cases, three of which, namely, the synergistic gangrenes, have already been referred to. The two largest groups are those of cellulitis and infected accidental wounds. Cellulitis is one of the characteristic manifestations of hemolytic streptococcal infections and the more virulent strains of hemolytic *Staphylococcus aureus*. The hemolytic streptococci are particularly susceptible to bacitracin but they are also susceptible to the sulfonamides and penicillin. However, for one reason or another a number of these cases had not responded to these other agents and we find, in studying the bacteriology of these 'Excellent' results, that more than half yielded on culture streptococci, either hemolytic, nonhemolytic, microaerophilic or anaerobic varieties which seemed to play a dominant role in the infection. We also find among these cases four in which a hemolytic *Staphylococcus aureus* was the principal organism and proved to be resistant to penicillin but susceptible to bacitracin. In one case in which there was a combination of hemolytic streptococcus and hemolytic *Staphylococcus aureus*, it was found that both of these organisms were susceptible to both penicillin

and bacitracin and, although 2,100,000 units of penicillin within 24 hours failed to stop the infection, it responded within another 24 hours to 20,000 units of bacitracin given every six hours.

There were 18 cases in the group in which bacitracin had no effect on the course of the infection. One of these was a post-hysterectomy pelvic cellulitis with necrosis of the vaginal vault which had failed to respond to

A



B

FIG. 4A.—Patient E.W.: Two months after bacitracin treatment and surgical excision. Full extension of fingers. B.—Patient E.W.: Two months after bacitracin treatment and surgical excision. Full flexion of fingers.

the sulfonamides, penicillin and streptomycin, and the patient was practically moribund when bacitracin was called for. Another case was a little girl of three who died from intestinal obstruction. This was caused by an abscess arising from a perforation of the tip of the appendix which was over on the left side and which surrounded and obstructed the sigmoid. Three patients with brain abscesses died without benefit of surgical drainage, bacitracin as

well as the sulfonamides and penicillin having failed to reach the focus in sterilizing concentration. In the other cases, the causative organisms were resistant to bacitracin. Two of these were staphylococci which were susceptible to penicillin and these patients responded to later treatment with penicillin. The other cases had a multiplicity of organisms, one with four, one with seven and one with nine different species, the majority of which were resistant to bacitracin.

When bacitracin was first discovered, we were not only impressed with the wide range of its antibacterial action but we were particularly happy to find that it appeared to have no toxicity for laboratory animals and gave no evidence of local irritation at the site of injection when surgical infections were so treated. In order to get away from extraneous factors and to develop a uniform product, we utilized a synthetic medium




FIG 5.—Patient V.H.: Osteomyelitis of stump of femur three years after receipt of battle wound, with two draining sinuses and three sequestra, before bacitracin treatment.

which yielded from 6 to 12 units of bacitracin per cc. at the peak of production on the third day of incubation. The concentrated antibiotic obtained from this medium showed no evidence of toxicity on repeated and prolonged periods of injection in our laboratory animals.

However, when the commercial firms were asked to prepare this antibiotic, they laid particular emphasis on finding a medium in which it could be produced in high titer. This was found in a medium made from soy bean flour which was cheap and easy to prepare and which yielded five to ten times as many units per cc. as the synthetic medium. When that product was sent to us for clinical and experimental study, we began to see evidences of

toxicity, most important of which in human cases seemed to be the development of traces of albuminuria and occasionally nausea and vomiting. A careful study of this material by Scudi and his associates <sup>7, 9, 10</sup> demonstrated some nephrotoxicity for mice and to a lesser degree for monkeys but none

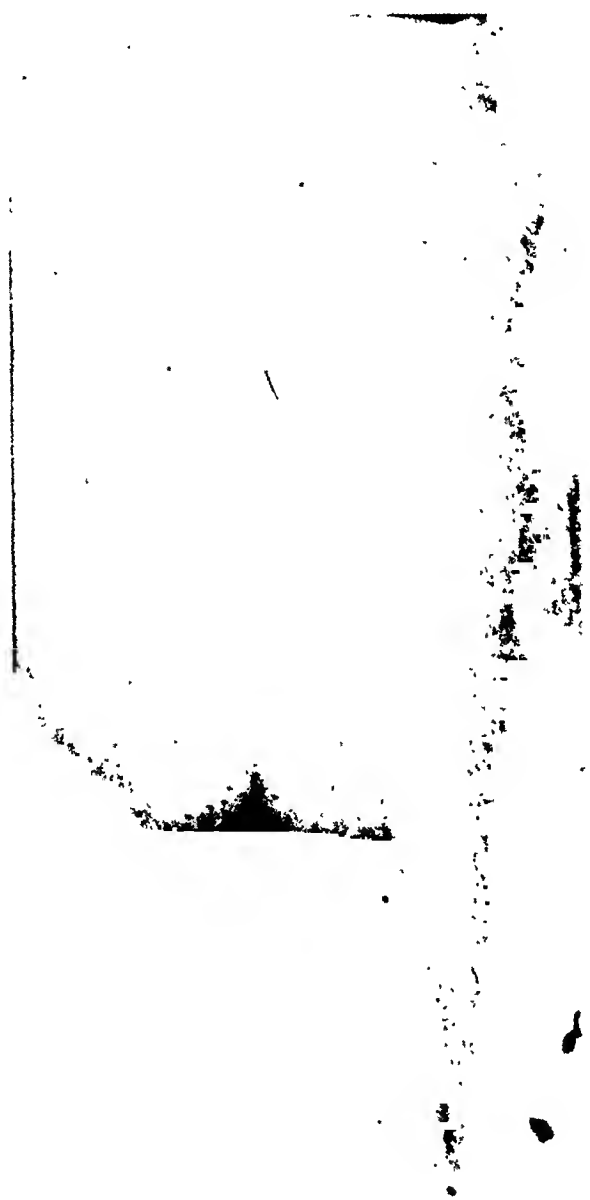


FIG. 6.—Patient V.H.: One month after excision of necrotic bone and removal of sequestra, with wound completely healed, after bacitracin treatment. Remaining foreign bodies in soft parts away from infected field.

at all for rabbits, rats and dogs. However, even in mice these kidney changes only occurred with very large doses well above the corresponding contemplated doses for man. Cautious use in human infections, produced a slight degree of albuminuria regularly, and occasionally abnormal cells and granular casts appeared in the urine, but we were happy to note that these abnormal

signs were transient and often disappeared during the course of treatment and that there was no appreciable rise in the nonprotein nitrogen or in the blood urea nitrogen. It was also observed that, if there was a persistence of any abnormality, it disappeared promptly after the termination of treatment.

TABLE II.—*Renal Excretion of Bacitracin—Patient V. H.*

Date	Specimen	Total MI	Units Per MI	Total Units	Intake (000)	Per Cent Excreted	pH	Albumen	Casts
1/29	24 hrs. ...	2050	13	26,650	...	...	7	0	0
1/31	24 hrs. ...	2300	30	69,000	132	52.3	6.5	st	0
2/1	18 hrs. ...	1270	30	38,100	99	37	6	ht	few
2/2	6 hrs. ...	800	60	48,000	...	...	7	t	few
2/3	6 hrs. ...	650	30	31,500	...	...	7	0	rare
2/4	24 hrs. ...	1900	20	38,000	132	28.7	7	0	0
2/5	24 hrs. ...	2100	40	84,000	132	63.6	7	spt	0
2/6	24 hrs. ...	1500	...	...	...	...	6.5	0	0
2/7	24 hrs. ...	1800	54	97,200	120	81	6.5	0	0
2/8	24 hrs. ...	1500	60	90,000	120	75	6.5	0	0
2/9	24 hrs. ...	1500	60	90,000	120	75	7	0	0
2/10	24 hrs. ...	1650	23	37,950	120	31.6	7	0	0
2/11	24 hrs. ...	1900	44	83,600	120	69.6	7.5	0	0
2/12	24 hrs. ...	2750	44	121,000	120	100	7.5	0	0
2/13	24 hrs. ...	2400	29	69,600	120	58	6	0	0
2/14	24 hrs. ...	2000	24	48,000	120	40	6.5	0	0
2/15	24 hrs. ...	1900	42	79,800	120	66	7	0	0
2/16	24 hrs. ...	2200	40	88,000	120	73.3	6	0	0
2/17	24 hrs. ...	1800	33	59,400	120	49.5	7.5	0	0
2/18	24 hrs. ...	1500	39	58,500	120	48	6.5	0	0
2/19	24 hrs. ...	2100	22	42,000	120	35	7.5	0	0
2/20	24 hrs. ...	2400	24	57,600	120	48	7.5	0	0
2/21	24 hrs. ...	2630	32	84,160	120	70.1	6	spt	0
2/22	24 hrs. ...	980	44	43,120	120	36	7.5	0	0
2/24	24 hrs. ...	2150	46	98,900	120	82.4	7.5	0	0
2/25	24 hrs. ...	2050	54	110,700	120	92.2	7.5	0	0
2/26	24 hrs. ...	1400	24	33,600	120	28	7	st	0
2/27	24 hrs. ...	2300	31	71,300	120	59.4	7.5	0	0
2/28	24 hrs. ...	2000	52	104,000	120	86.6	7.5	0	0
2/29	24 hrs. ...	1800	33	59,400	120	50	7.5	0	0

spt—Smallest possible trace.

st—Slight trace.

t—Trace.

ht—Heavy trace.

TABLE III.—*Renal Excretion of Bacitracin—Patient J. L.*

Date	Specimen	Total MI	Units Per MI	Total Units	Intake (000)	Per Cent Excreted	pH	Albumen	Casts
2/16	Before ...	120	0	0	0	0	..	0	0
2/16	Dose 1 ...	170	21	3,570	...	...	...	spt	0
2/17	18 hrs. ...	600	37	22,200	80	27.75	6.5	st	rare
2/19	24 hrs. ...	1000	34	34,000	80	42.5	7	ht	occ.
2/20	24 hrs. ...	1300	34	44,200	80	55.2	5	ht	mod.
2/21	24 hrs. ...	1200	38	45,600	80	57	5	ht	mod.
2/22	24 hrs. ...	750	46	34,500	80	43.1	4.5	ht	occ.
2/24	24 hrs. ...	2050	40	82,000	80	102.5	4.5	ht	mod.
2/25	24 hrs. ...	995	54	53,730	80	67.1	4.5	ht	many
2/26	24 hrs. ...	1300	33	42,900	80	53.6	4.5	t	mod.
2/27	24 hrs. ...	1000	35	35,000	80	..	4.5	t	mod.
2/28	24 hrs. ...	1060	11	11,600	0	..	4.5	st	occ.
2/29	24 hrs. ...	1400	0	0	0	0	4.5	st	occ.
3/3	... ..	....	..	....	..	..	4.5	spt	0

spt—Smallest possible trace.

st—Slight trace.

t—Trace.

ht—Heavy trace.

This was the experience of all the units working with bacitracin and we began to have a sense of confidence in the safety of the drug, which we felt would permit effective clinical doses without any evidence of damage to the kidneys. Two illustrative cases are shown in the accompanying Tables II and III.

It was at this point that the Food and Drug Administration set up the temporary specifications of bacitracin, mentioned above, which were considered an adequate safeguard against injury to the patients.

About the first of the year, the methods of production and all of the material produced by surface growth in bottles by the Ben Venue Laboratories of Bedford, Ohio were taken over by the Commercial Solvents Corporation. The Ben Venue Laboratories had been furnishing us with our material and during the first two months of this year their stock-pile was gradually turned over to us by the Commercial Solvents Company in quantities as we needed it and it was used up on these patients. In February we

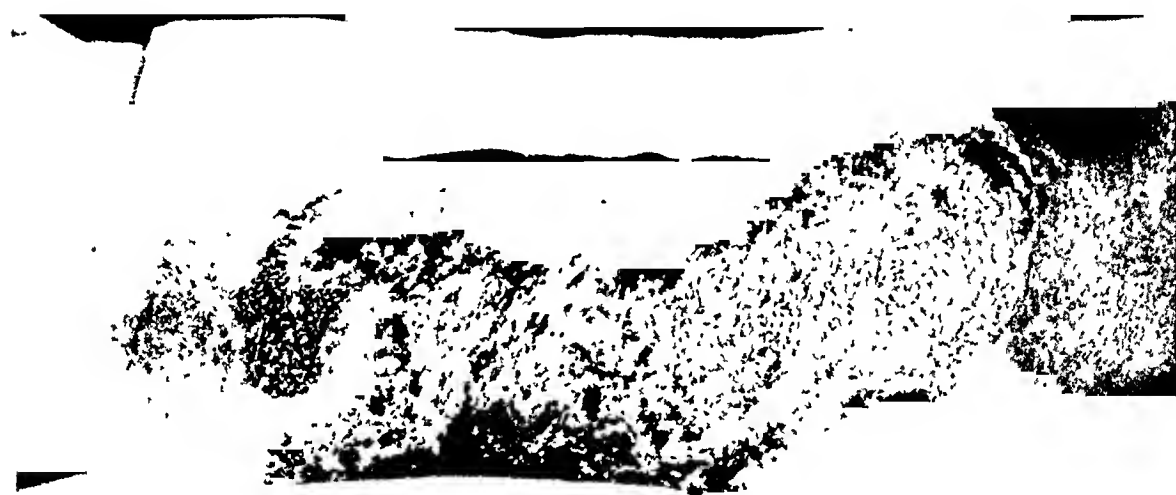


FIG. 7.—Patient A.W.: Bacterial synergistic gangrene of four months' duration, following hysterectomy, lesion involving lower half of abdomen and both thighs, before bacitracin treatment.

began to receive bacitracin made by the Commercial Solvents Corporation by the deep tank method, and then, for the first time, one of the units began to notice more pronounced evidences of nephrotoxicity than we had seen before with higher degrees of albuminuria and more cellular abnormalities, a higher rise in retained nitrogen and symptoms of lassitude on the part of the patient. Soon afterward these same results were observed in other units and in one case there was a temporary renal shut-down while in another there was an irreversible rise in blood urea nitrogen.

The case with the renal shut-down occurred in a patient with an extensive and rapidly spreading cellulitis of the neck which had not responded to penicillin. The causative organism was not obtained but the clinical activity of the organism indicated a hemolytic streptococcus. He was given double the usual primary dose of bacitracin and this was administered every four hours for the first 24 hours. The infection promptly came under control so that it is listed among the 'Excellent' results. However, after the cessation of treatment and after the patient returned home, he noticed a decrease in

the output of urine and a general lassitude which brought him back to the clinic. Here it was found that he had albumin in the urine and a rise in blood urea nitrogen and therefore he was admitted to the hospital for study. Gradually his urinary output rose to normal although the specific gravity remained low. His blood urea nitrogen came down to normal levels.

The toxicity of the presently available commercial product is under very close study. There are a number of facts which indicate that the toxic factors



FIG. 8.—Patient A.W.: Synergistic gangrene wound completely epithelialized, seven weeks after starting bacitracin.

are by-products of manufacture, particularly of the deep tank method, and they appear in certain batches of the preparation but not in all. It is hoped and expected that they will be eliminated in the near future.

The exact chemical nature of bacitracin has not yet been determined although studies are being pursued in this direction in several different laboratories. We know that it is made up of a number of amino acids although it does not have the properties of a pure polypeptid. Some of these amino acids may be unnatural and thus give rise to nephrotoxicity, as is known to be the case with d-serine. It may be possible to eliminate these unnatural amino

acids without interfering with the antibiotic effect or it may be possible to neutralize their nephrotoxic action by some chemical means. For example, it has been demonstrated that a number of salts can greatly reduce the toxic action, among these are sodium chloride, sodium bicarbonate and sodium sulfate. In the administration of the antibiotic, therefore, for the time being

BACITRACIN BLOOD LEVEL

DOSAGE: 20,000 UNITS EVERY SIX HOURS

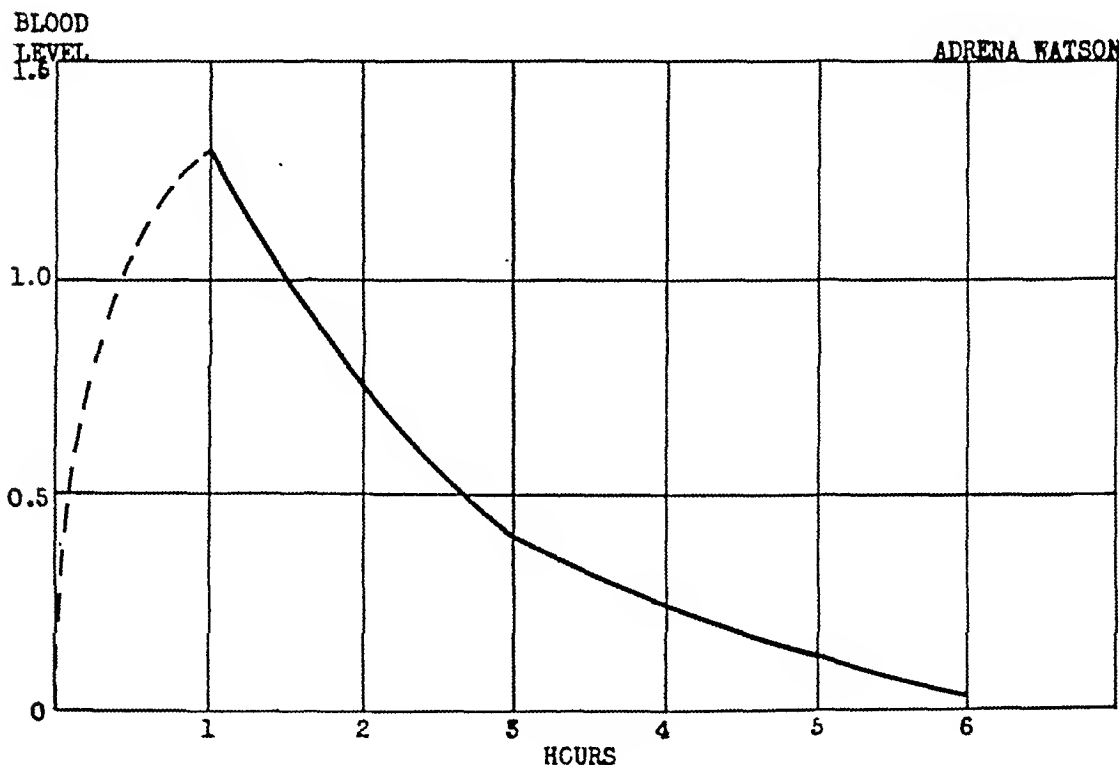


FIG. 9.—Patient A.W.: Bacitracin blood level after intramuscular injection of 20,000 Units.

the solvent should contain one or another of these salts. It is the present practice to dissolve the lyophilized product in 2 per cent novocaine made up in normal saline, and to alkalinize the patient so that the urine is always at a pH of 6 or more.

It is well known that individual animals and certainly individual human beings vary considerably in their reaction to all of these antibiotics and some persons may have an idiosyncrasy to them or develop an allergy to them. So far, these reactions have been minimal with bacitracin.

SUMMARY

1. The new antibiotic bacitracin may be used systemically as well as locally in the treatment of surgical infections.
2. Specifications have been set up by the Food and Drugs Administration to safeguard its use in clinical cases.
3. The results in 105 cases of surgical infections treated by the systemic



administration of the new antibiotic have been presented. These represent a wide diversity of conditions but for the most part they were cases which had failed to respond to the sulfonamides and to the other antibiotics.

4. There was an overall favorable response in about 70 per cent of these cases and, in about one-fifth of these, the results were dramatic.

5. Of particular interest were three cases of extensive progressive bacterial synergistic gangrene, all of whom responded within 72 hours and recovered without the necessity for surgical excision.

6. In the three largest groups, namely, "cellulitis", "deep abscess" and "infected accidental wound", favorable results were obtained in 78 per cent of the cases.

7. In the dramatic group, the causative organisms were for the most part in the staphylococcal and streptococcal groups. In the latter classification, were found hemolytic, nonhemolytic, microaerophilic and anaerobic streptococci. In a considerable number of staphylococcal strains, we found a resistance to penicillin and a susceptibility to bacitracin.

8. In 14 per cent the results were questionable and in a slightly higher percentage, the results were frankly nil. In most of these cases the causative organisms were resistant to bacitracin.

9. In the majority of the patients in the whole series there was a transient albuminuria which disappeared either during continued treatment or soon after treatment was discontinued.

10. Some of the later preparations of bacitracin made by the deep tank method have shown evidence of nephrotoxicity. New specifications will have to be drawn up to detect these toxic factors. When the presently available bacitracin is used systemically, there should be repeated tests of kidney function pathology and treatment should be discontinued if there is any indication of serious damage.

11. However, with doses which are not damaging to the kidneys, favorable and sometimes dramatic results may be expected in surgical infections caused by organisms which are susceptible to bacitracin. This covers a wide range of bacteria which are commonly found in surgical infections.

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DISCUSSION.—DR. E. P. LEHMAN, Charlottesville, Va.: I want to report briefly on some work with bacitracin that is being carried on in our laboratories by Dr. William R. Sandusky under the guidance of Dr. Meleney. This work is concerned with the use of bacitracin in experimental clostridial infections. The experiments were performed by exposing muscle in guinea pigs, crushing it, and closing the wound. After the wound was closed, varying amounts of *Clostridium Welchii* were injected into the area of damaged muscle and a number of the animals were treated with varying doses of bacitracin.

There were 44 control animals, of which only 17 survived. I want to point out that 26 animals died of gas gangrene with the usual picture of an enormously swollen leg and the other phenomena with which we are all familiar. One died of other causes. In the 93 animals treated with bacitracin, none died of *C. Welchii* infection. There were 25 deaths from other causes—pneumonia, persistent diarrhea, and in one or two instances intestinal obstruction as the result of intussusception. The number surviving was 68. Counting in the deaths from other causes the mortality rate is 59 per cent in the controls and 27 per cent in the bacitracin treated animals, which presents a statistically significant difference. In those animals that died of other causes there was no evidence of *C. Welchii* infection at autopsy. Leaving out the animals that died of other causes, there is no mortality in the bacitracin treated series and a mortality of 59 per cent in the animals that had no bacitracin.

At the time these experiments were done there was a good deal of disease in the guinea pig colony and it is not possible to say that this relatively large number of deaths in the experimental series had anything to do with the drug itself. The fact that they did not occur in the other series might suggest that it was a toxic factor in the drug, but I should like to hear Dr. Meleney's comment on that. The results in any event appear to suggest strongly that bacitracin has a specific effect in the prevention of clostridial infection in the guinea pig.

DR. I. S. RAVIN, Philadelphia: I should like to review a few impressions we have obtained with the use of bacitracin in the project under Dr. Meleney that Dr. Zintel is heading in our clinic. The clinical results of systemic administration of bacitracin have been encouraging but there can be no doubt, as Dr. Meleney said, and Dr. Lockwood re-emphasized, that bacitracin is nephrotoxic for man. Dr. James Mitchie of our Section in Urology has been studying the possibilities of renal injury with this substance. Four patients have been extensively studied for evidence of renal, hepatic and blood cytology toxicity and have uniformly shown moderately severe renal tubular injury.

One patient who received 3,744,000 units of bacitracin over a period of 13 days had a 66 per cent reduction in tubular function; one month later the tubular function was still 22 per cent below the premedication value. A second patient receiving 200,000 units of bacitracin daily for 10 days had an 85 per cent reduction in tubular function:

12 days after bacitracin was discontinued the tubular function was still 66 per cent below pre-medication value. The observations of Dr. Meloney and Miss Johnson, that the nephrotoxicity of the bacitracin preparation does not parallel the antibiotic potency does suggest, as he has said, that the nephrotoxic factor is not a part of the bacitracin molecule. Until improved methods of manufacture eliminate the nephrotoxic factor, we must move very cautiously in further systemic use of this substance, for there can be no doubt that the renal injury is not a short-lived one in many of these patients, but persists over a very considerable time.

DR. CHAMP LYONS, New Orleans: Beginning rather cautiously a year ago when this problem was first presented to us, namely, that of deciding between bacitracin therapy for penicillin-resistant infections and the extension of other methods, we proposed to try combined therapy. We had already begun to vary the interval of dosage, and for the past eight months we have routinely used a dosage of penicillin every eight hours, as prescribed by Dr. Altmeier, with complete satisfaction to ourselves.

Instead of treating penicillin-resistant infections with bacitracin, we elected to use mixed therapy, because the evidence in the literature suggests very strongly that any antibiotic of bacillary origin will have inseparably produced in that mixture some nephrotoxic constituents. Until that problem is solved we have decided not to use any antibiotics of bacillary origin. We have used mixtures of penicillin, streptomycin and sulfadiazine, with an eight hour interval for doses of penicillin and streptomycin for penicillin-resistant infections with, I believe, quite satisfactory results.

DR. FRANK L. MELENEY, New York (closing): I appreciate very much the interest shown in the presentation, and thank the discussors for bringing up these points. Certainly the toxicity of bacitracin is of great importance and concern. I want to say a few words to indicate why I think this is not a factor of the bacitracin itself, but one of the byproducts of manufacture. In the first place, the material we made in our laboratory with a synthetic medium showed no evidence of toxicity whatsoever.

The manufacturers began the preparation of bacitracin with the same method which we had used in the laboratory and one of them sent us a small quantity of material which likewise showed essentially no toxicity. However, the yield per cc. in this medium was not satisfactory from a commercial standpoint and the manufacturers began using a soy-bean medium. In this medium bacitracin was produced in five to ten times as high a titre per cc. All commercial lots so far have been made in this medium but, along with the bacitracin, toxic factors came through in the final product. However, the material made by the Ben Venue Laboratories by means of surface culture in bottles produced only transient albuminuria and temporary rises in retained nitrogen. We were becoming quite complacent about the importance of toxicity inasmuch as we were able to obtain a clinical response without appreciable evidence of kidney damage. Most of the cases reported in this paper were treated with bacitracin from this source. However, recently we have been using bacitracin made by the Commercial Solvents Corporation by the deep-tank method and, while we have been told that in all other respects the manner of manufacturing is essentially the same, this material is certainly giving more frequent and more prolonged toxic symptoms. Furthermore, different lots vary considerably in their toxicity. This is true of lots having the same potency titre. We know that the toxicity is greatly modified by the salt content. In our animal tests bacitracin dissolved in physiologic saline is very much less toxic than bacitracin dissolved in distilled water.

Bacitracin has not yet been obtained in a pure state but chemical analyses indicate that it is made up of a number of amino acids, some of which are natural while others are unnatural. The toxicity may likely be in the unnatural amino acids which

may be either removable or neutralizable. When bacitracin is put in the ultracentrifuge, certain heavy products are carried down which are toxic, while the bacitracin remains evenly distributed. Furthermore, a dialyzing membrane will hold back certain toxic products which are obviously not a part of the antibiotic itself. The toxicity problem will be very intensively studied in the course of the next two or three months.

It is surprising to me to hear Champ Lyons say that almost all of the infection problems can be met by combined therapy of the sulfonamides with either penicillin or streptomycin. Certainly many infection problems come to me which have failed to respond to all of these agents. In fact, many of the cases reported in this paper are in this category. Dr. Lehman's report on the work of Dr. Sandusky with gas gangrene is of particular interest and clearly indicates that bacitracin is able to prevent the development of gas gangrene in experimental animals. The late deaths of some of the survivors may be indicative of toxicity of this particular lot of bacitracin, or it may be due to some factor associated with the culture material used in the injection. The control animals did not live long enough to show these late effects. Until this toxic problem is solved it is essential that the systemic treatment of bacitracin should be administered only in those units which are properly set up for its appraisal and in those cases which have not responded to the other available methods for the treatment of infections.

# PARALYSIS OF DEGLUTITION – SURGICAL CORRECTION

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THIS PRESENTATION HAS TO do with reconstructive work necessary to restore the power of swallowing in a patient who has sustained extensive cranial nerve injuries. In 1864, Hughlings Jackson<sup>1</sup> called attention to the homolateral paralytic association of larynx, soft palate, tongue and muscles of the neck, particularly the sternomastoid and trapezius. In 1891, Avellis<sup>2</sup> wrote on palate laryngeal hemiplegia, a syndrome which sometimes bears his name. Since then additional articles by Schmidt,<sup>3</sup> Tapia,<sup>4</sup> Broeckaert,<sup>5</sup> have stressed certain features resulting from involvement of the last cranial nerves.

Particularly Vernet<sup>6</sup> and Collet<sup>7</sup> in 1915 have written on the syndrome of the jugular foramen characterized by involvement of the last three or four cranial nerves. In 1917 Villaret<sup>8</sup> used his term, "the syndrome of the retroparotid space," and included lesions of the sympathetic together with the last four cranial nerves. From World War I similar injuries have been reported.

## CASE HISTORY

The patient, a white male 43 years of age, presented himself with the complaint of an inability to swallow dating from the time of a gunshot wound three years before. The wound of entrance of a 38 calibre bullet was alongside of the left ala of the nose and from there the bullet had passed directly back to a position just beneath the scalp, 1 cm. to the left of the external occipital protuberance (Fig. 1). In its course the mandible on the left had been fractured. Tremendous hemorrhage was presumably due to division of the internal jugular vein, and he required several transfusions. A long period of infection about the jaw ensued and union was considerably delayed; some months were required before healing was complete. The bullet had injured and caused a paralysis of several nerves (Fig. 2). The anterior two-thirds of the tongue on the left was anesthetic from injury of the lingual branch of the trigeminal. Farther posteriorly, near the jugular foramen, it had encountered and paralyzed the ninth, tenth, eleventh and twelfth cranial nerves. As a result of the paralysis of the twelfth nerve, the left half of the tongue, in addition to being anesthetic, was atrophic. By reason of paralysis of the tenth nerve, the palatal movement on the left was absent and the left vocal cord was paralyzed so that his voice was hoarse, and the upper, middle, and inferior pharyngeal constrictors were paralyzed. With paralysis of the eleventh nerve, the supply to the left sternomastoid and trapezius was affected. The damage to the ninth nerve was responsible for anesthesia of the soft palate, nasopharynx and pharynx on the left. The stylopharyngeus muscle, which is the only muscle supplied by that nerve, was paralyzed.

Since the time of the injury the patient had been unable to swallow. He had learned to adjust himself and had become fairly well adapted to this, maintaining a

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\* Read before the American Surgical Association, May 29, 1948, Quebec, Canada.

fair state of nutrition with a liquid diet and regular use of a stomach tube. His most serious complaint was of strangling from excessive salivation. Since he was unable to swallow the saliva, it passed frequently into his larynx. This caused terrific explosions of coughing and vomiting, with regurgitation of the material into the nasopharynx and through his nose. Even with continued use of such drugs as atropine to lessen the amount of secretion, travel in public conveyances was almost prohibited because of the frequency and severity of these attacks. The patient was on the point of suicide.

It was apparent at once that numerous factors contributed to his disability. In the act of swallowing, the tongue rises and presses upward and backward; the soft palate closes off the nasopharynx, the larynx rises and its opening is covered by the epiglottis as the material passes into the upper portion of the esophagus. During and after World War I, occasional reports

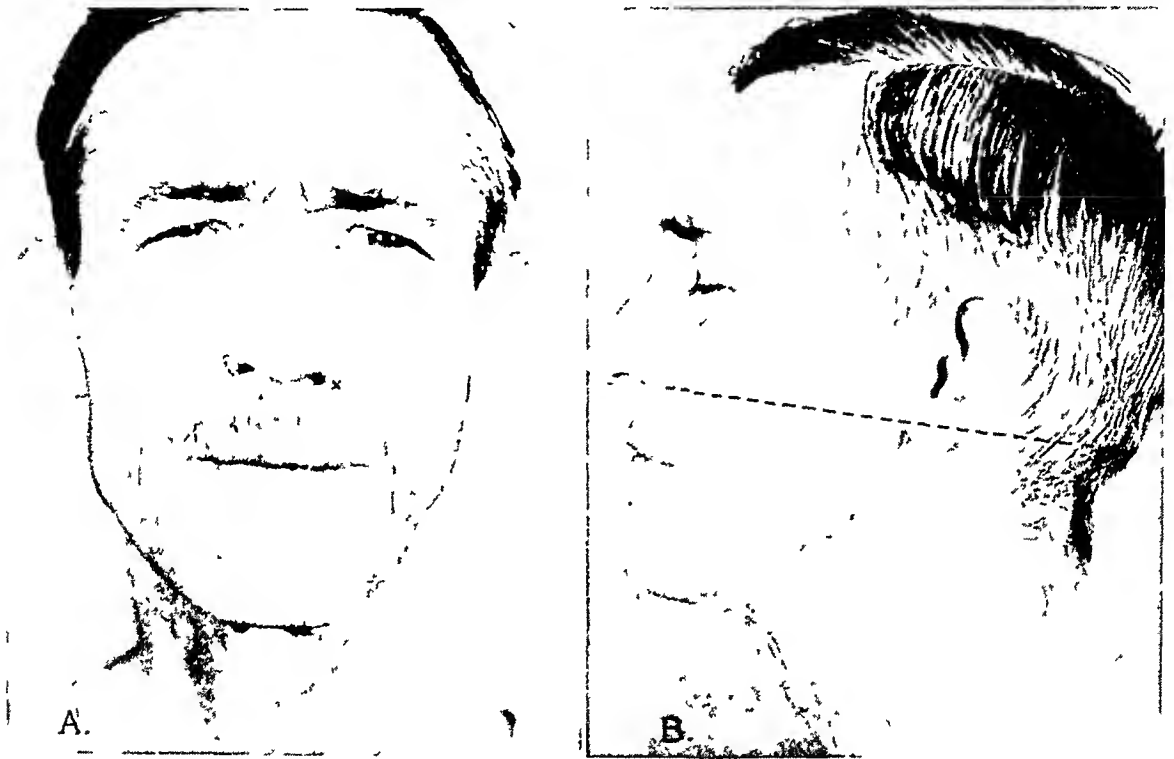


FIG. 1.—Showing course of bullet.

describing extracranial paralysis of the last four cranial nerves from bullet wounds appeared in the literature. We have been unable to find evidence of any surgical treatment which corrected such an inability to swallow.

Beginning with Majendi's work in 1813,<sup>9</sup> various theories of deglutition have been advocated. Majendi believed that ingested materials were forced from the mouth into the stomach by means of peristaltic-like muscular contractions of each area through which the bolus passed and that in effect the muscles of the mouth, pharynx and esophagus were active agents in propelling the food onward. He considered there were three stages: (a) a voluntary stage during which the mylohyoid and longitudinal lingual muscles contracted and enabled the tongue to propel the bolus past the fruces; (b) an involuntary, almost convulsive contraction of the pharyngeal constrictors

during laryngeal elevation which forced the material into the upper end of the esophagus and finally, (c) a slower, involuntary stage during which the bolus was driven along into the stomach by the esophageal circular fibers. In 1880 Kronecker and Falk<sup>10</sup> suggested that fluids and semifluids were projected by contraction of the muscles of the mouth (the mylohyoids) before the contraction of the pharyngeal and esophageal musculature occurred, and that this occurred later after the bulk of the bolus had passed and served to sweep along the remaining particles. Kronecker reported that

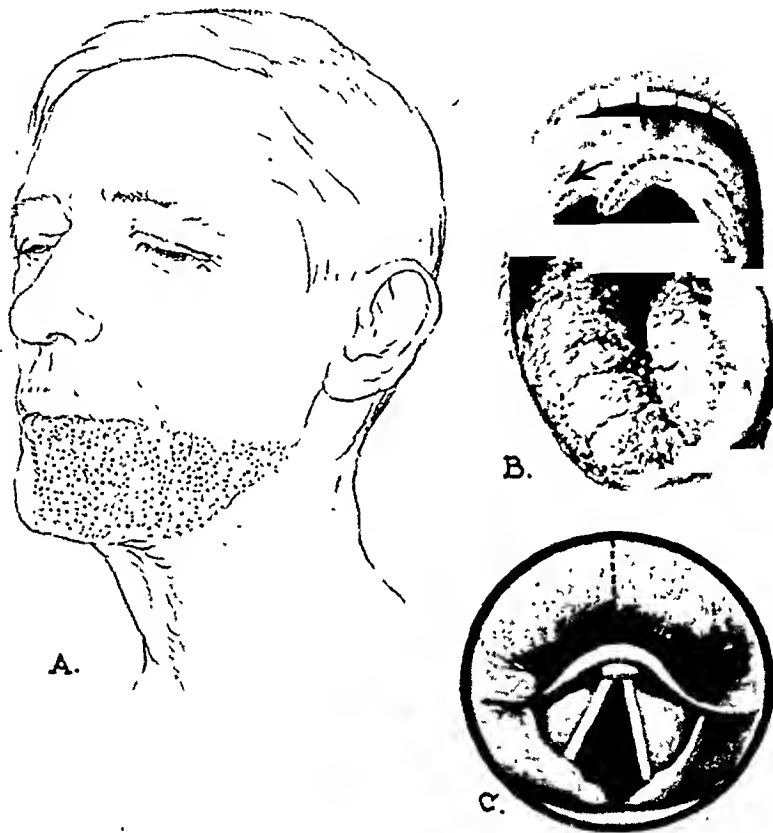


FIG. 2.—A. Dotted area of altered sensation from injury to inferior dental nerve and cervical branches. B. Atrophy of left half of tongue (twelfth nerve injury); deviation of uvula (tenth nerve); outline of anesthesia (ninth nerve). C. Adducted position of vocal cord (tenth nerve).

at the beginning of deglutition there was a rapid rise of manometric pressure, to 20 cm. of water, in the posterior mouth, pharynx and upper esophagus. By means of balloons in the pharynx and esophagus, they recorded the passage of the peristaltic wave some time after the descent of the ingested liquids.

Cannon,<sup>11</sup> in 1898 and 1900, showed that the act of swallowing varied

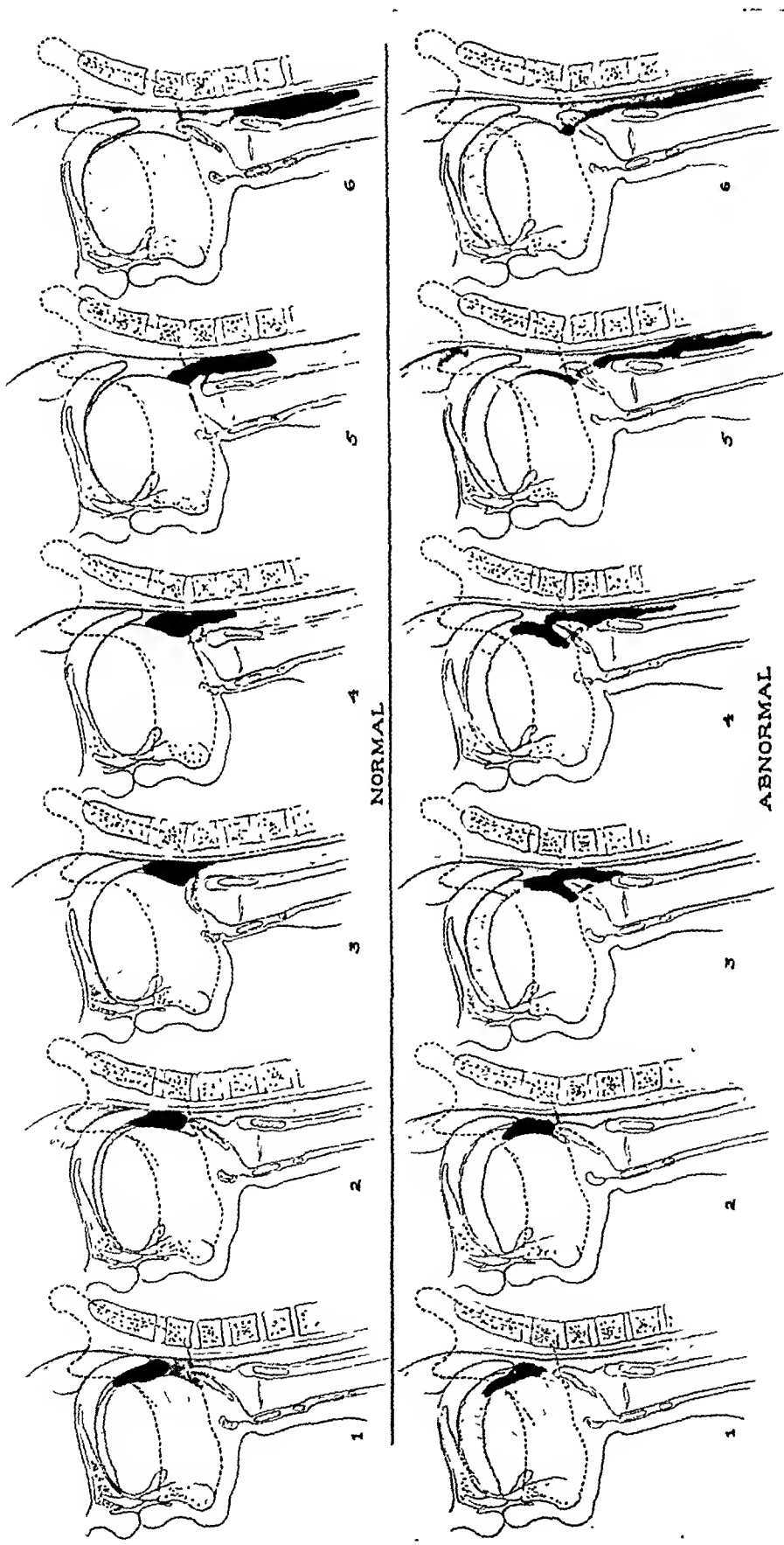


FIG. 3. NORMAL.—1 and 2. Bolus pressed against the soft palate occluding nasopharynx. 3 and 4. Tongue pressing up and back; larynx ascends; epiglottis occludes laryngeal opening as bolus passes; 4 and 5. Bolus passing into esophagus. 6. Larynx descended, epiglottis upright, bolus in esophagus. ABNORMAL.—1 and 2. One half of tongue atrophied; nasopharynx not closed off by palate. 3 and 4. Oral cavity and nasopharynx not closed by tongue; larynx has ascended only partially; epiglottis remains upright. Bolus has passed into valleculae and pyriform sinus. 5 and 6. Bolus gradually trickles into esophagus.



with different vertebrates and with different consistencies of the ingested material. By means of roentgen-ray studies, he came to the conclusion in agreement with Kronecker and Meltzer, that in the human fluids were shot directly down to the cardia, mainly by the action of the mylohyoids and not by peristalsis, but that the swallowing of solids and semisolids was a slower peristaltic-like process. Deglutition in fowls was relatively slow and peristaltic and there was no mylohyoid squirting action. In the absence of such action a greater reliance on gravity was noted. For example, in dogs when the mylohyoids were denervated, fluids were no longer rapidly squirted into the esophagus, but it was necessary for the animal to raise its head and swallow, after the manner of a bird. In the horse and in man, it has also

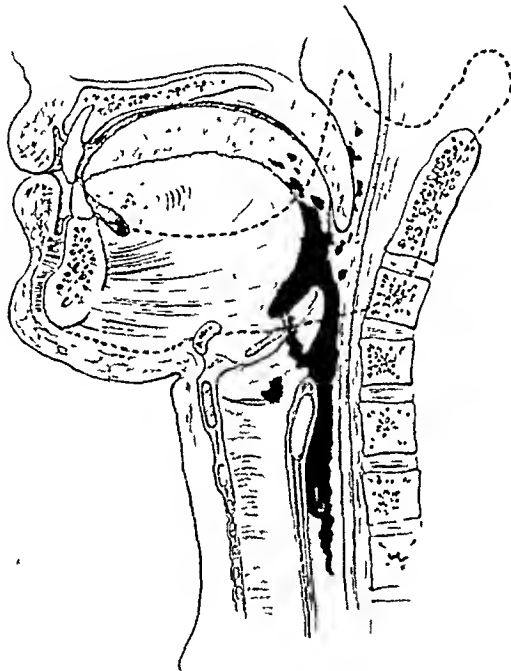


FIG. 4.—Barium scattered by coughing.

been noted that only fluids were squirted ahead by the mylohyoids before the peristaltic action occurs. Cannon described human swallowing of a solid bolus thus: When the food is sufficiently masticated, it is gathered in a depression on the dorsum of the tongue. The tip and lateral aspects of the tongue press against the hard palate and teeth, to prevent escape of food particles forward and laterally to the mouth and cheeks. Respiration is reflexly suspended. The tongue is pressed upward and backward by contraction of the mylohyoid and hyoglossus respectively (Fig. 3 Normal). The tongue, thus acting as a piston, drives the bolus first against the downward

sloping soft palate, next against the posterior pharyngeal wall, then on between this pharyngeal wall and the posterior surface of the upright epiglottis, the tip of which lies in contact with the base of the tongue. During this phase the action of the palato-pharyngeus muscles has thrown the pharynx into a narrow cleft and against this opening the soft palate is pulled by contraction of the levator palati, thus blocking entrance of the bolus into the nasal chambers. Thus far the esophageal opening has remained closed mainly by pressure of the larynx against it. With the rise of the hyoid and larynx, the esophagus opens. The epiglottis is pressed back until it shuts the laryngeal aperture. Then presumably the tip of the epiglottis

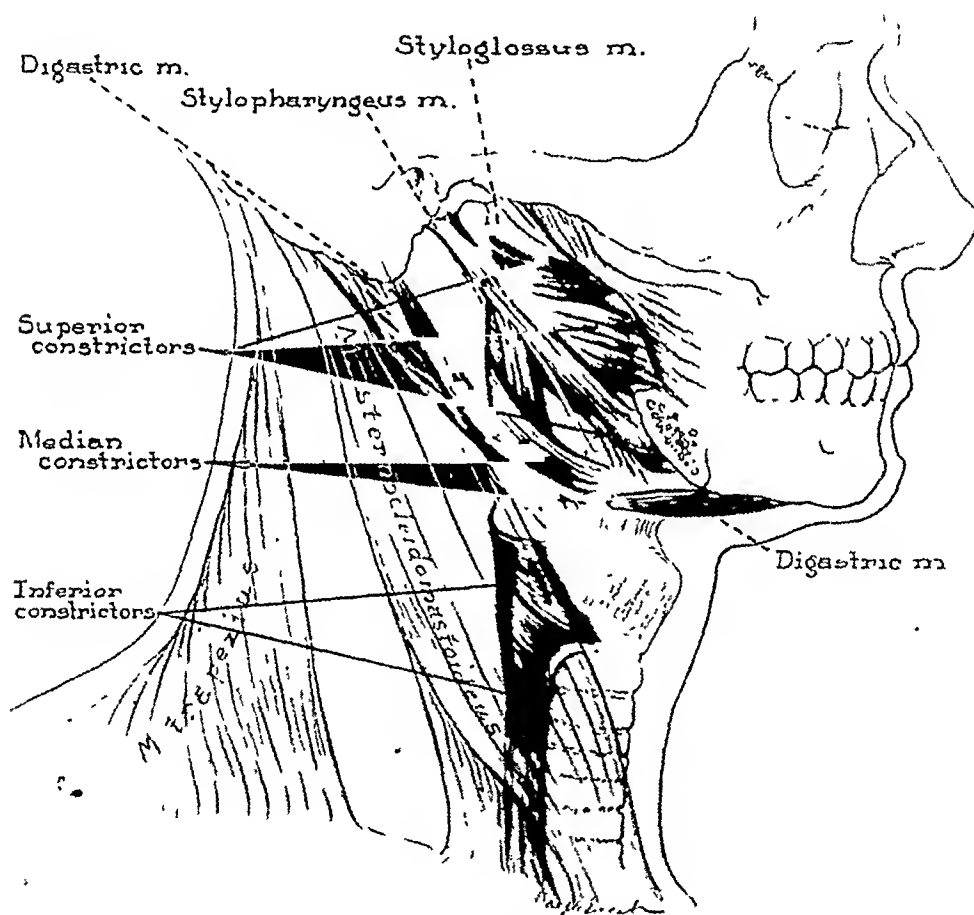


FIG. 5.—Final attachment of the posterior belly of the digastric in the human.

slips downward along the posterior pharyngeal wall, "pushing the bolus probably with a final quick impulse into the gullet." Whether or not the action of the epiglottis is a factor in pushing the bolus is a point that was disputed as far back as 1892 by Stuart.<sup>12</sup> Mosher,<sup>13</sup> in 1927, published studies from which he concluded that the epiglottis acts as a cover for the larynx during swallowing.

Fluoroscopic studies of our patient by Dr. Earl Miller demonstrated that the paralyzed pharyngeal constrictors bulged outward during the swallowing

effort and that barium accumulated and remained in the valleculae of each side of the base of the epiglottis. It was also apparent that the epiglottis remained upright and did not pass into a horizontal position to occlude the laryngeal opening. The barium trickled down from the valleculae on each side into the pyriform sinuses and occasionally small flecks passed into the larynx. Explosive efforts at coughing followed and observation after this showed flecks of the material scattered throughout the pharynx and in the

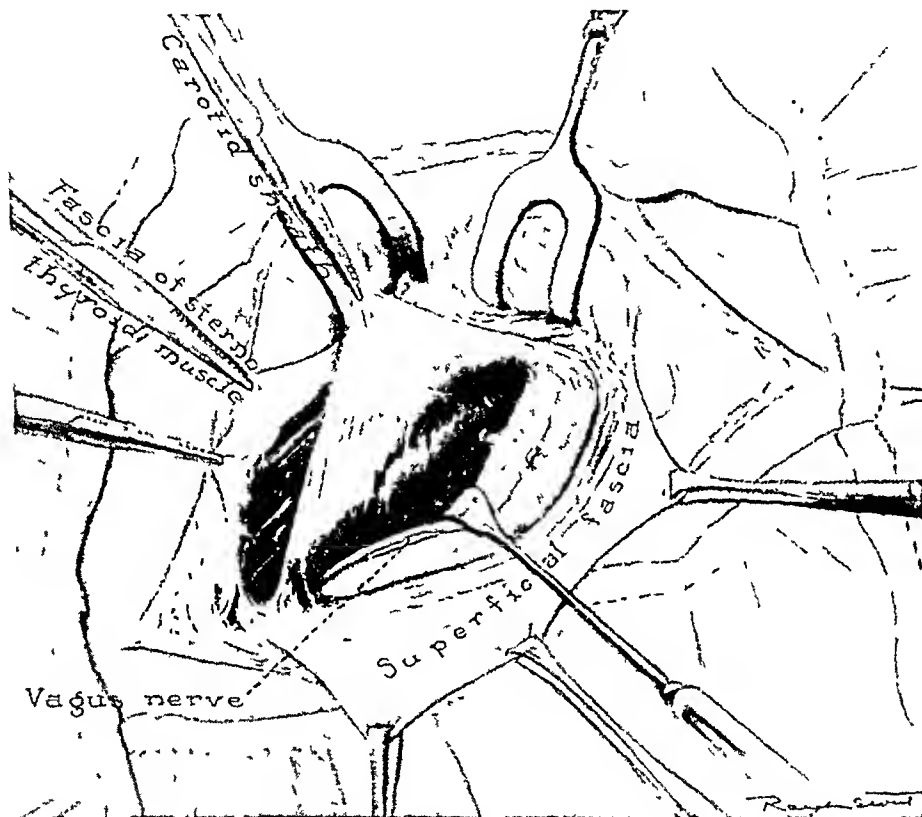


FIG 6—Fascial support of the lateral wall of the pharynx.

avrious pockets and in the nasopharynx (Fig. 4). The entire act of swallowing is so rapid that more detailed analysis was impossible. We found it necessary to secure more data on the normal act of swallowing before a satisfactory analysis could be made of the difficulties of our particular patient.

We were able to obtain the use of a fluoroscope synchronized with moving picture apparatus so that with this cine fluoroscope radiograms of deglutition could be taken at the rate of 60 to the second. Such studies were obtained of a normal individual and then upon our patient. It was possible then to study the motions of swallowing at intervals of one-sixtieth of a second and to compare the abnormal function with the normal (Fig. 3 Abnormal). It became evident that at least one important factor was that which prevented the epiglottis from assuming a horizontal position and closing the larynx during the act of swallowing. Although the larynx would rise during the

act of swallowing, its upward excursion was less than normal. The stylopharyngeus muscle, which is the only one supplied by the ninth nerve, passes down from the styloid process and inserts in the region of the larynx between the superior and middle pharyngeal constrictors. Its action in drawing the larynx upward had been lost through its paralysis. Other contributing factors were the bulging of the paralyzed pharyngeal constrictors on that

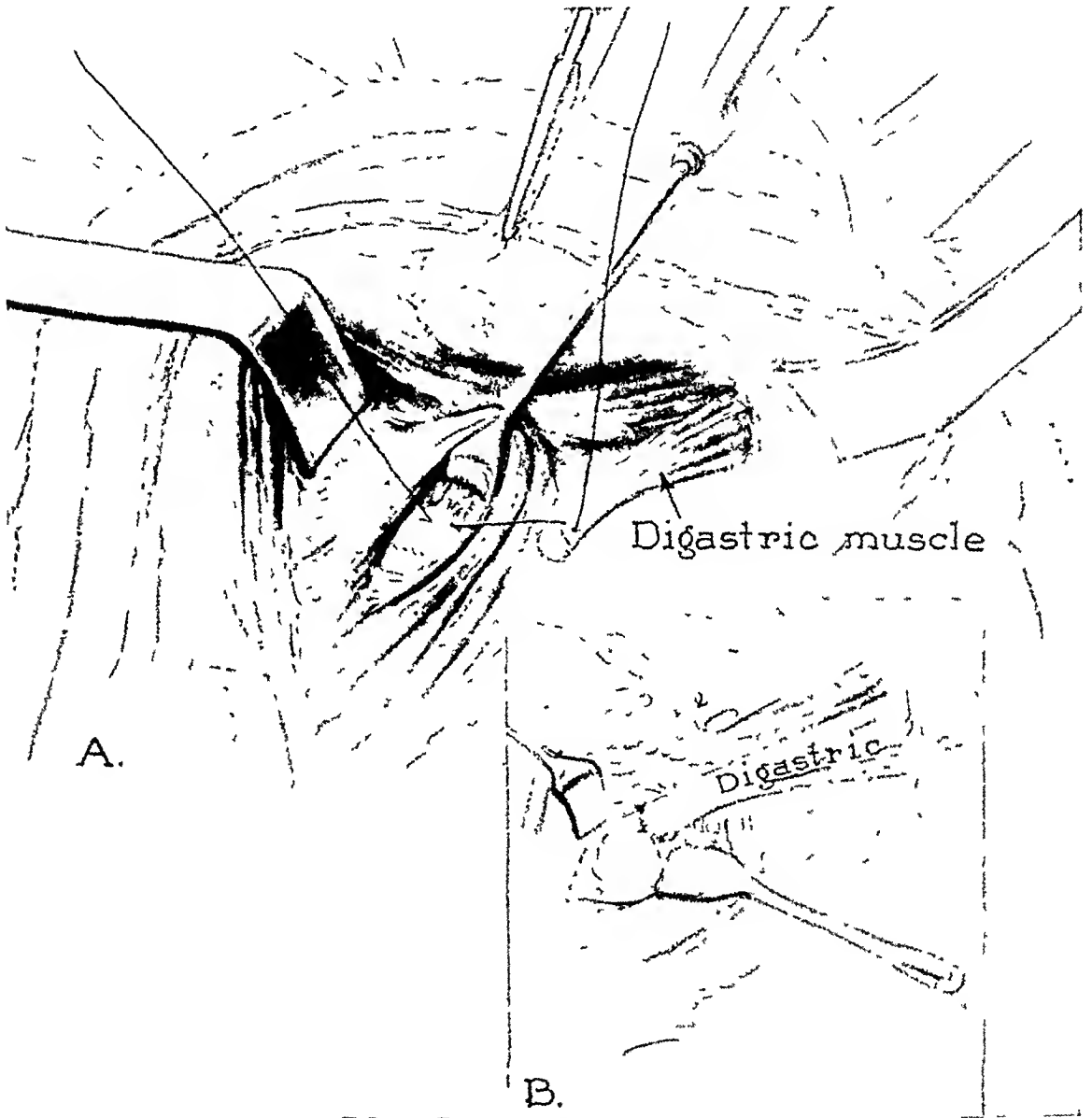


FIG. 7.—Digastric divided at the sling. Posterior belly sutured to laryngeal cartilage.

side and atrophy of the tongue. The pressure of the tongue on the epiglottis, which carries it down to a horizontal position, was impaired.

It seemed desirable, then, to reproduce the neurologic lesion in experimental animals and endeavor to find a solution for the difficulty. The anatomic arrangement in the dog was not suitable, but the macaque was found to be an appropriate animal. A similar lesion was produced by paralysis of the ninth, tenth, eleventh and twelfth nerves. Following this, the animal retained food in its mouth for 12 hours and was unable to

swallow. To prevent the lateral bulging of the pharynx, a fascial sling was devised which was attached to the prevertebral fascia posteriorly, then brought around the lateral pharyngeal wall and attached to the midline of the laryngeal and neighboring cartilages. In order to aid the upward movement of the larynx during swallowing, the posterior belly of the digastric, which is innervated by the seventh nerve, was attached to the larynx to substitute for the paralyzed stylopharyngeus (Fig. 5). This was done in the animal and was followed by restoration of the ability to swallow. The

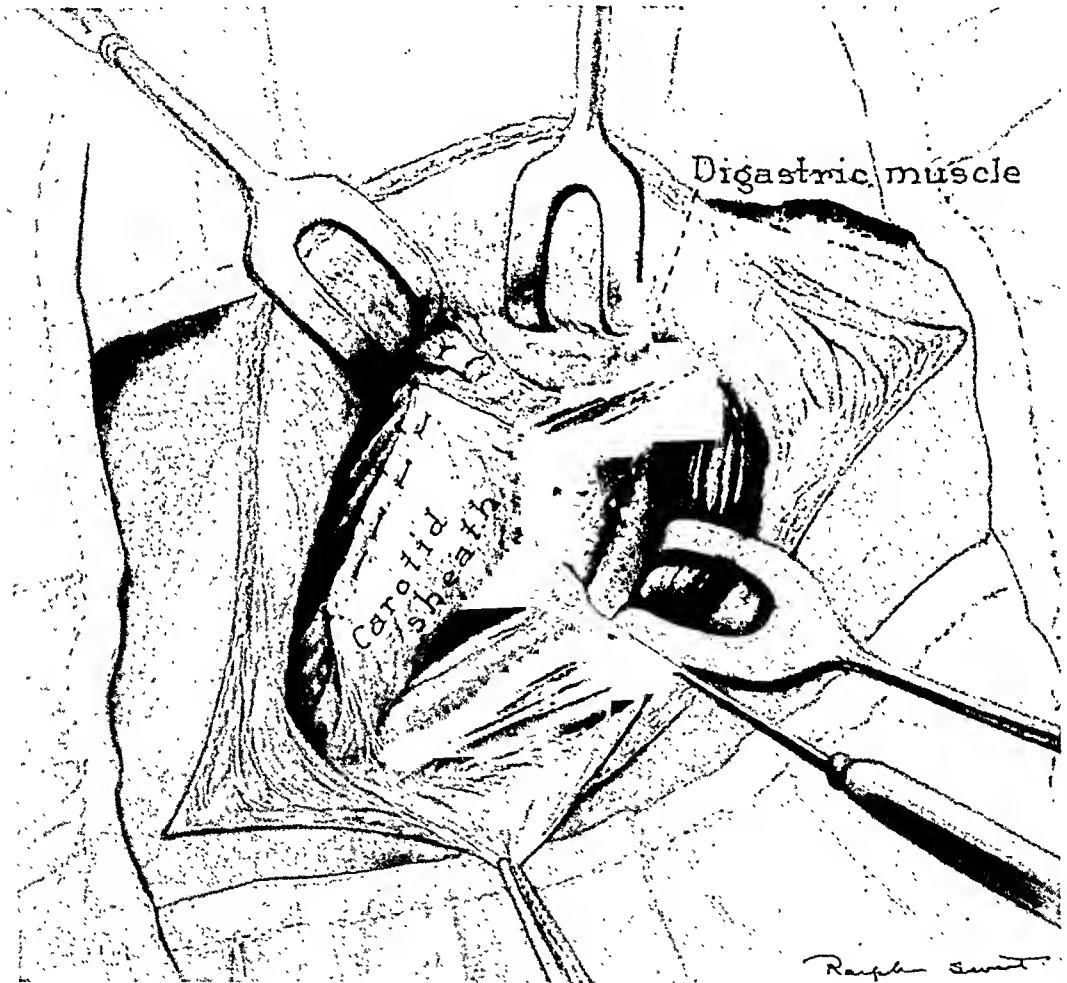


FIG. 8.—Carotid sheath reflected and sutured to midline to support the pharyngeal wall.

procedure was then planned for the human patient. (The seventh nerve was unimpaired.)

It was found that the use of a free fascial sling to wrap around the pharynx was not required, for by splitting the fascia of the neurovascular bundle from in front (Fig. 6) and dissecting away the mesial portion of it to its firm attachment to the prevertebral fascia, a free leaf was obtained which was then brought forward around the pharynx and fastened to the

midline of the larynx and cricoid. This gave firm support to that side of the pharynx. The posterior belly of the digastric was then cut loose from its junction with the anterior belly and firmly attached to the thyroid cartilage (Fig. 7) so that its contraction would cause ascent of the larynx. During the postoperative period the patient was taught to so grimace with the lower face that the digastric contracted at the instant of swallowing. By this maneuver, the larynx was elevated and the patient was trained to swallow. It has now been over two years since the operation and there has been no occasion to have recourse to the stomach tube. Swallowing is sufficiently satisfactory that the patient has been able to work in construction camps and partake of the more or less rough food which is available.

Advice, suggestions and help on the anatomic details and studies have been given freely by Professor Saunders of the Department of Anatomy. Research by the roentgen-ray studies has been carried out by Dr. Earl Miller.

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DISCUSSION.—DR. MAX PEET, Ann Arbor: I was much intrigued with this paper when Dr. Naffziger kindly allowed me to read it in advance, because I could see applications for this procedure in cases other than the very rare gunshot wounds. Occasionally we have tumors in the posterior fossa which produce almost identical symptoms because of paralysis of the vagus and, in some cases, of the hypoglossal in addition.

The difficulty in swallowing that these people experience is often their chief complaint. Many of these patients come to us so late that, although the tumor can be removed successfully, there is no chance for regeneration and, as you see the patient months and even years afterward, he begs for something to be done to aid him in swallowing. True, most of them do not have as much difficulty as this patient of Dr. Naffziger's, but they do have regurgitation of food into the nasopharynx, sometimes it even shoots out of the nose, or down into the larynx, and they have severe fits of coughing. This new operative procedure developed by Dr. Naffziger may be of great benefit to some of these patients.

However, it would not be of value in patients having great difficulty in swallowing and from whom very large acoustic tumors have been removed, because in such cases the 7th nerve has also been destroyed. This would preclude the use of the digastric muscle to elevate the larynx. This use of the digastric muscle in Naffziger's operation is a very clever method of elevating the larynx. Some other method will have to be found in individuals who have paralysis of the 7th as well as the 10th nerve.

I am particularly pleased to have this clear elucidation of the act of swallowing, a complicated procedure which was not understood before this splendid demonstration. The application of this special x-ray camera, taking pictures at one-sixtieth of a second, clearly demonstrates the actual process of swallowing. I am not sure of how much importance paralysis of the stylopharyngeus muscle is. Certainly in individuals with glossopharyngeal neuralgia we do not hesitate to divide the entire 9th nerve intracranially, which would include its motor branch to the stylopharyngeus muscle. These individuals do not have any difficulty in swallowing. I have divided both 9th nerves for bilateral glossopharyngeal neuralgia and no impairment in swallowing was evident. Perhaps the stylopharyngeus in the normal individual does act as the chief elevator of the larynx. However, in individuals with this muscle paralyzed, but without any other intracranial pathology, other muscles probably take over that function. In the case described by Dr. Naffziger the paralysis was so extensive that no regular muscle function could be substituted.

I do not know what other muscle could be used in place of the digastric to elevate the larynx, but certainly the fascial sling Dr. Naffziger devised to hold in the bulging pharyngeal muscles and prevent the pocketing which held so much food would be applicable. I am very much pleased that Dr. Naffziger had this opportunity to make such an important contribution.

# LATE COMPLICATIONS FOLLOWING CRANIOPLASTY WITH ALLOPLASTIC PLATES\*

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A COLLECTION OF STATISTICS on complications following cranioplasty with alloplastic plates was undertaken for presentation at the round-table discussion on cranial injuries held at the Clinical Congress of the American College of Surgeons in September 1947, under the chairmanship of Dr. A. Earl Walker. These have been augmented and further clarified during the intervening months. It is a pleasure to express my thanks and appreciation to the neurosurgeons of the Army, Navy, and Veterans Administration hospitals who have been so helpful in the collection of these data. In answer to a questionnaire, case reports were obtained on 151 late complications following the insertion of plates of tantalum, vitallium, and acrylic resin, which came into standard use in our military hospitals during the War.

An excellent article on the history and development of cranioplasty was published by Woolf and Walker<sup>1</sup> in 1945. They have reviewed past experience with the various technics for grafting bone and cartilage and experiments in the use of a great variety of strange materials such as horn, ivory, hard rubber, mica, plaster of Paris, etc. Early successful results are reported with silver, gold and celluloid. Silver through oxidation becomes mildly irritant; both it and gold are expensive and too soft for use in large plates. Silver has the added disadvantage of ultimately discoloring the overlying scalp. With the exception of celluloid, used with success by Ney<sup>2</sup> and Coleman,<sup>3</sup> plating with these substances had dropped out of use between the wars.

Tantalum came into use in 1941 after Burke<sup>4</sup> reported its use for buried surgical appliances and sutures and after the demonstration of its suitability for cranial repairs by Pudenz,<sup>5</sup> Hook<sup>6</sup> and Fulcher<sup>7</sup>. The first use of vitallium for repair of cranial defects was described by Geib<sup>8</sup>, also in 1941. The use of methyl methacrylate resin (lucite or plexiglass) was developed experimentally by Kleinschmidt<sup>9</sup> and adapted to human cranioplasty in this country by Gurdjian et al<sup>10</sup> and by Kahn<sup>11</sup> in 1943. At the time of Woolf and Walker's review sufficient time had not elapsed to permit any survey of late complications from the use of these alloplastic plates which have proved to be so convenient for repairing such huge cranial defects as can be made by an airplane propellor, shell fragment, or kick of a horse. These concave gaps in the skull are unsightly, a source of risk from further trauma, and may give rise to much local discomfort and apprehension. Yet many questions in connection with their repair remain unanswered. What is the best materials to use? When is the best time for its insertion? What

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\* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.



are the risks of displacement, late infection, cerebrospinal fluid leaks, pneumatocele, and epilepsy? These questions could not be answered in 1945 when Woolf and Walker's report was published. It is of interest also to note that plating with alloplastic material was never approved by the National Research Council. It has therefore been a stimulating challenge to attempt to obtain an answer to the late results of the great number of cranioplasties performed in the war two to six years after these plates were inserted.

#### SUMMARY OF REPORTED FAILURES

In July, 1946, Bradford and Livingston<sup>12</sup> reported eight patients seen at the Naval Hospital in Oakland who required early removal of tantalum plates because cranioplasty had been performed at too early a date in an infected field. These repairs had failed to heal and had drained persistently from the start. That late breakdown of the scalp was occurring following cranioplasty with plates of biologically inert metals and acrylic resin in a small proportion of cases first became apparent from a review by Lane and Webster<sup>13</sup> of the combined experiences at 22 Veterans Administration hospitals where 52 plates had been removed prior to April, 1947. In the series of 196 patients operated upon on Dr. C. W. Elkins' service at the Newton D. Baker General Hospital and followed by Dr. Thomas Holbrook (personal communication) up to their discharge from the Army, 6.1 per cent are known to have required removal of plates for secondary infection, and a total of 11.7 per cent had complications which required some form of surgical intervention. Experience at the Special Military Hospital for Head Injuries in Oxford has shown that 8.5 per cent of cranial defects repaired by tantalum plates have developed complications necessitating their removal in a two-year period of observation. These statistics are based on a review of 128 patients in whom 130 tantalum plates were inserted. Lewin, Graham, and Northcroft<sup>14</sup> were able to follow all but four of these men over a minimal period of two years, and have been kind enough to send me a copy of their manuscript prior to its publication. Although it has been impossible for the Office of the Surgeon General of the Army or the Bureau of Medicine and Surgery of the Navy to furnish statistics on the total number of cranioplasties performed in our military hospitals, I believe it is fair to assume that less than 10 per cent have been unsatisfactory. From the 151 reports of late complications summarized in Table I, together with the evidence submitted in the Oxford report, we are justified in drawing certain definite conclusions regarding the use of plates in the repair of cranial defects:

1. Complications from plates made of tantalum, vitallium, and lucite occur in practically the same proportion of cases. In Elkin and Holbrook's series these amounted to 10.6 per cent in 66 cranioplasties performed with lucite and 12.3 per cent in 130 after plating with tantalum.

2. Thin, scarred and inadequately vascularized scalp is likely to break down over a plate (Fig. 1).

3. Poorly fitted plates, or those that have not been securely fixed and have slipped, may erode the scalp (Fig. 2). The use of triangular metal points for fastening the plate have been a frequent cause of this complication. Vitallium or tantalum screws are superior, but even these can become loose if the plate has not been properly fitted and exerts constant traction on the screw.



FIG. 1.—Thin, poorly vascularized scalp, which broke down at junction of two poorly constructed flaps sutured under tension to cover defect over vitallium plate.

The plate beneath was drilled in hopes that granulations would grow through from underlying dura. This failed and plate was finally removed; prompt healing followed.

Resultant scar was so firm that no secondary plate was needed to cover 4 cm. defect in skull.

(Patient of Dr. J. C. White, U. S. Naval Hospital, St. Albans )

4. Plates should be perforated at frequent intervals to permit escape of underlying fluid and its absorption by the lymphatics of the scalp; also in order to secure better fixation by fibrous union between the dura and galea. A number of surgeons reporting have commented on the frequency of complications in unperforated plates. In a few instances, solid plates giving rise to trouble have been successfully replaced immediately after multiple

drill holes were made. Ulmer reports from the McGuire V. A. Hospital (personal communication) that plates, if properly perforated, may even heal in place after separation of the overlying scalp. In four complications where the scalp broke down because of scar formation and infection, the plates "healed over with the assistance of buds of tissue growing up through the perforations while the infection was controlled by antibiotics."

5. Perforations in the dura-arachnoid may result in leakage of spinal fluid around the plate and require secondary repair (Fig. 3). The im-



FIG. 2.—Large, poorly fitted plate, whose prominent lower edge compressed and eroded scalp. Removal of plate and partial closure were followed by uneventful but slow healing  
(Courtesy of Dr. Loyal Davis, V A. Hospital, Hines, Mich )

portance of water-tight dural closure to prevent accumulation of cerebrospinal fluid under the plate has been emphasized in the Oxford report. Lewin et al<sup>14</sup> have even suggested that the presence of a metallic plate may lead to excessive secretion.

6. Plates inserted over the frontal sinus or mastoid may lead to trouble if air leaks into the tissue or there is secondary acute infection. Harris and Woodhall<sup>15</sup> have reported two instances of extradural pneumatocele from residual defects of the frontal sinus. I have information on one case

of late infection around a supraorbital plate following acute frontal sinusitis. In a previous review of complications with 52 plates which necessitated removal, Lane and Webster,<sup>13</sup> neurosurgical consultants in the Veterans Hospital at Dearborn, Michigan, have found that in approximately half frontal plates have been at fault (Fig. 4). Furthermore, in 18 of these the defect involved the frontal sinus. In those cases reported in Table I in which the position of the plate is known, frontal plates gave rise to one-third of



FIG. 3.—Small defect from imperfect dural closure, which permitted persistent reaccumulation of cerebrospinal fluid under vitallium plate. After fascial patch plate was replaced. Healing and late result have been satisfactory for over two years.

(Courtesy of Dr. T. I. Hoen, U. S. Naval Hospital, St. Albans.)

the complications. The inadvisability of repairing defects which involve the frontal sinus and brow ridge is confirmed in this larger series and also in the Oxford report.

7. Trauma to scalp over the plate and also secondary plastic operations have resulted in loss of overlying tissue and necessitated removal (Fig. 4). In one instance the plate was actually stove in as a result of direct trauma in an automobile accident.

8. There have been a few reports that metallic plates have caused discomfort on exposure to extreme heat or cold. Figure 5 illustrates such a complication with shifting of the loose plate as an added factor. Substitution of an acrylic plate securely anchored by screw fixation has given a satisfactory result.



FIG. 4.—Erosion of thin tissue over brow ridge with infection and exposure of tantalum plate, following a secondary plastic procedure. Removal of plate and evacuation of epidural abscess were followed by uneventful healing. (Courtesy of Dr. Loyal Davis, V. A. Hospital, Hines, Mich.)

9. The onset of convulsive seizures secondary to cranioplasty with alloplastic plates is not a complication to be feared. Epilepsy unquestionably due to the presence of a plate has been reported in only a single case observed by Dr. Hannibal Hamlin from the U. S. Naval Hospital at Chelsea (personal communication). In this patient a plate had previously been inserted to cover a 5 cm. defect three months after drainage of a cerebral abscess. Latent infection developed and the plate was removed, but the surgeon made the mistake of inserting tantalum foil to cover the dural defect. This sailor developed severe convulsions. On re-exploration the tantalum foil was removed together with a dense fibrous scar tightly adherent to underlying brain. The dural defect was reconstructed and a new tantalum plate fitted. He has remained seizure free on dilantin for two years.

In a certain proportion of these cases there is no explanation for the appearance of swelling and tenderness over the plate months after its insertion other than reactivation of latent primary infection. In many of these cases it has been obvious that the plate was inserted too early following healing of an infected wound. In some roentgen rays revealed the presence of indriven bony fragments and metallic foreign bodies which had not been

removed. Dr. T. I. Hoen (unpublished cases seen at U. S. Naval Hospital, St. Albans), like Bradford and Livingston, had to remove five of these plates in patients in whom cranioplasties had been performed at too early a date in advanced hospitals in the Pacific. In addition, Woodhall, Pilcher, German, Meirowsky, and others (personal communications) have observed instances where cranioplasty was performed at too early a date. It is evident that Gardner's<sup>16</sup> suggestion of primary plating at the time of operation for active

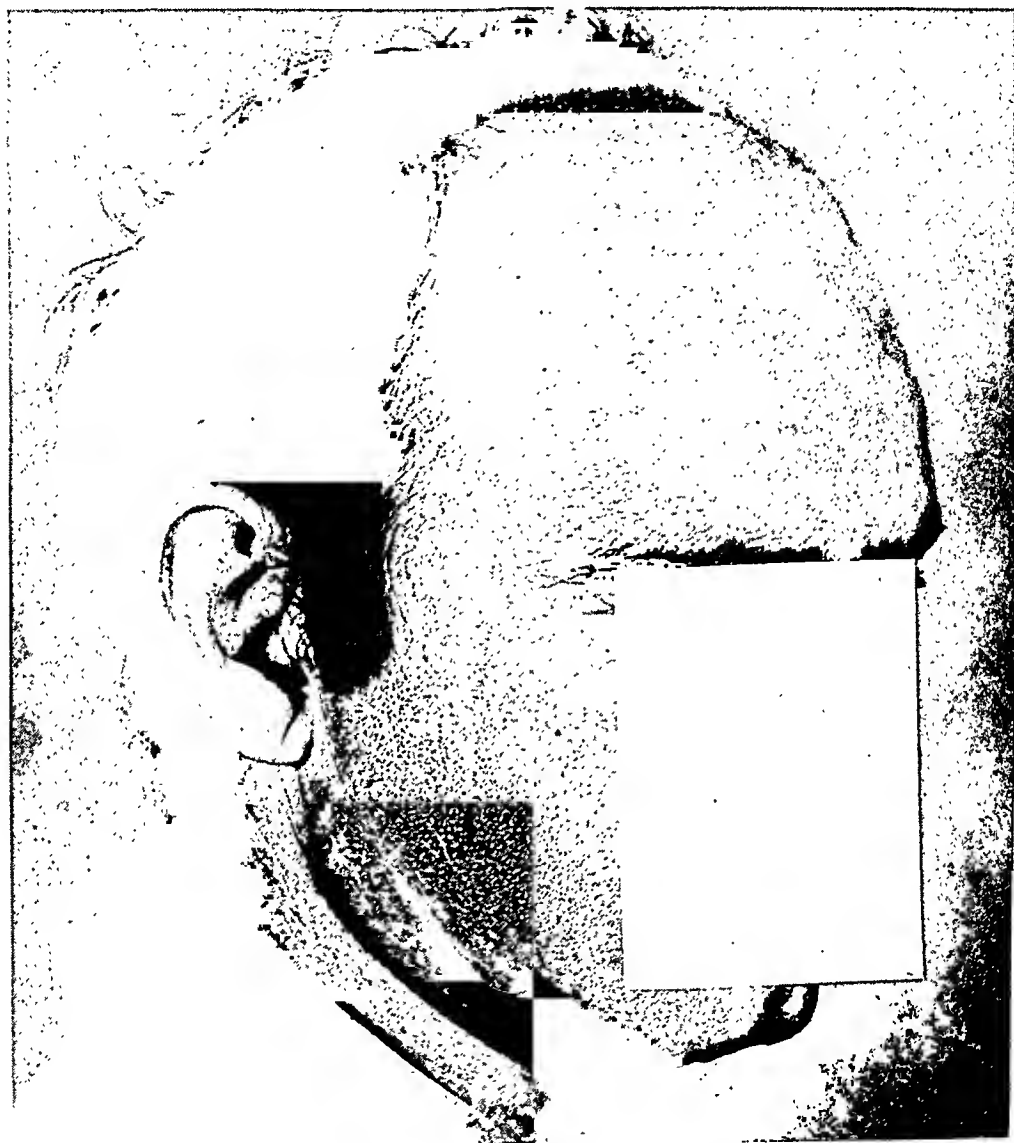


FIG. 5.—Tantalum plate covering defect in frontal bone, which had slipped and caused discomfort on exposure to heat and cold. This was replaced by acrylic resin plate fixed in place by screws, with satisfactory result. (Courtesy of Neurosurgical Service, Cushing V. A. Hospital, Framingham, Mass.)

osteomyelitis and cerebral abscess is a definite departure from sound surgical principles.

Fortunately infection that has developed around these plates has usually been mild and osteomyelitis of the exposed bone in the edge of the defect has never been a serious problem. In patients where the repairs have broken

TABLE I.

CASES REPORTED FROM													COMMENT
	Total No. of Cases	Infected	Non-Infected	Plate Preserved	Plate Removed	Later Re-plating	Loss of Secondary Plate	Frontal Plates Causing Complications	Pneumatocele	Brain Abscess	Death	Epilepsy due to Complication	
U.S.N.H., Chelsea, Mass. .... (Dr. H. Hamlin)	2	1	1	..	2	..	..	1	..	..	..	1	Seizures due to cerebral cicatrix around tantalum foil used for dural substitute.
U.S.N.H., Oak Knoll ..... (Dr. W. J. German)	6	6	..	1	5	..	..	..	..	..	..	..	
U.S.N.H., St. Albans (Drs. J. C. White and T. I. Hoen)	10	8	2	1	9	1	..	..	..	1	1	..	Pt. with abscess moribund on admission.
Newton D. Baker Gen. Hosp, W.Va. (Dr. Thomas Holbrook)	23	20	3	11	12	..	..	..	..	..	..	..	Material: 66 lucite, 130 tantalum.
Aspinwall V.A.H., Pa. .... (Dr. S. N. Rowe)	2	2	..	..	2	..	..	..	..	..	..	..	
Bronx V.A.H., N.Y. .... (Dr. E. G. Krueger)	11	10	1	..	11	1	..	4	1	1	..	..	Cortical abscess formed under tantalum foil used to cover defect in dura.
Crile V.A.H., Cleveland, O. .... (Dr. P. P. Partington)	3	1	2	1	2	1	..	1	..	..	..	..	Cerebrospinal fluid leak through dural defect. Another plate stove in by trauma.
Cushing V.A.H., Framingham, Mass. (Neurosurgical Service)	5	5	..	..	5	..	..	3	..	..	..	..	One tantalum plate replaced by lucite because patient claimed disagreeable sensation heat and cold.
Dearborn V.A.H., Mich..... (Dr. G. S. Bates)	3	3	..	..	3	..	..	2	..	..	..	..	One infection due to acute frontal sinusitis.
Hines V.A.H., Mich. .... (Dr. L. Davis)	14	14	..	..	14	1	1	..	..	..	..	..	
Jefferson Barracks V.A.H., Mo.... (Dr. R. D. Woolsey)	4	3	1	..	4	..	..	1	..	..	..	..	One plate exposed by trauma; one broke down because of retained cotton pledget; one poor fit.
Kennedy V.A.H., Memphis, Tenn... (Dr. A. M. Meirowsky)	5	5	..	..	5	1	..	1	..	..	..	..	Two epidural granulomas suggested toxic reaction.
Lawson V.A.H., Chamblee, Ga. ... (Dr. G. Perret)	5	5	..	1	4	2	..	2	..	..	..	..	
Los Angeles V.A.H., Calif. .... (Dr. W. A. Jones)	4	4	..	1	3	1	..	1	..	1	..	..	..Abscess caused by retained loose fragment of bone.
McGuire V.A.H., Richmond, Va.... (Dr. J.L. Ulmer)	12	10	2	6	6	..	..	1	..	..	..	..	Two non-perforated plates replaced at once after drilling.
Mendota V.A.H., Madison, Wis.... (Dr. L. E. Trent)	1	1	..	..	1	..	..	..	..	..	..	..	
Miami Beach V.A.H., Fla. .... (Dr. W. T. Haverfield)	4	1	3	2	2	2	..	1	..	..	..	..	
Minneapolis V.A.H., Minn. .... (Dr. H. F. Buchstein)	1	1	..	..	1	..	..	1	..	..	..	..	
Salt Lake City V.A.H., Utah .... (Dr. R. Harrow)	1	1	..	..	1	1	..	..	..	..	..	..	
Wadsworth V. A. H., Kan. .... (Dr. L. T. Gathman)	1	1	..	..	1	..	..	..	..	..	..	..	
Washington V. A. H., D.C. .... (Dr. H. V. Rizzoli)	2	..	2	1	1	..	..	1	..	..	..	..	Sharp edge of fixation point eroded scalp, cerebrospinal fluid leak around tantalum point.
White River Junction V.A.H., Vt... (Dr. H.L. Heyl)	3	3	..	..	3	..	..	..	..	..	..	..	One plate slipped so that it indented dura.
Winter V.A.H., Topeka, Kan. .... (Dr. L. L. Bernstein)	2	2	..	..	1	..	..	1	..	1	1	..	Death from infection following primary plating at another hospital. Patient entered moribund with abscess under temporal plate.
Wood V.A.H., Wisconsin ..... (Dr. D. Cleveland)	5	5	..	..	5	1	1	..	..	..	..	..	
Dr. W. McK. Craig, U.S.N. Hosps..	1	1	..	..	1	1	1	..	..	..	..	..	
Dr. E. F. Fincher, U.S.A. Hosps...	8	8	..	4	4	1	..	..	..	..	..	..	
Dr. H. C. Naffziger, San Francisco.	1	1	..	..	1	..	..	..	..	..	..	..	
Dr. C. Pilcher, Nashville .....	4	4	..	..	4	..	..	..	..	..	..	..	
Dr. B. Selverstone, U.S.A. Hosps...	3	3	..	3	..	..	..	..	..	..	..	..	
Dr. B. Woodhall, U.S.A. Hosps. ...	5	3	2	3	2	..	..	2	2	..	..	..	..Successful pedicle graft to cover defect.
151 132 19 35 115 14 3 23* 3 4 2 1													

\* These 23 occurred in 69 cases where the location of the plate was specified.

down, simple removal of the plate together with underlying granulations and devitalized bone or loose fragments, followed by primary closure (with or without brief drainage), chemotherapy and local and systemic penicillin, has usually resulted in prompt healing. If the cranial defect has been a small one, fibrosis has usually made secondary plating unnecessary, but it can be carried out successfully after a delay of six months to a year. Only three out of 14 secondary plates have been lost.

Two deaths have resulted from the insertion of plates which may be ascribed to definite errors in surgical judgment. One occurred in a late neglected spreading suppuration around a plate inserted overseas. This sailor arrived moribund at St. Albans with an underlying intracerebral abscess. The other, reported from a Veteran's Hospital, had had a plate inserted immediately following late secondary debridement of osteomyelitis and a granulating wound with loose bony fragments. He was discharged soon thereafter, but re-entered another hospital in a moribund condition from underlying abscess of the brain. Two other abscesses beneath plates have been reported from the Veterans' Hospitals. These have responded well to early and adequate drainage.

#### LESSONS TO BE DERIVED FROM EXPERIENCE OF WORLD WAR II

There are certain obvious lessons that we should learn from these experiences. Late complications, as shown above, have occurred most frequently after plating the frontal bone, especially in reconstructions of the orbital ridge. To construct and secure in place a perfectly fitting plate in this area is a difficult technical feat. In addition, this region is particularly susceptible to trauma and infection from the frontal sinus and nasal cavity. Complications from these sources are likely to occur as long as the patient lives. Breakdown of the thin skin in the upper eyelid with infection of the plate occurred in one nervous individual who picked at a prominence over the edge of his plate while studying. Reconstruction by bony grafts is not as likely to make trouble on these scores, and I think we should consider a change in policy in this type of cranioplasty. From what I have learned from this review I shall henceforth use grafts of autogenous bone for repair of the orbital ridge, but continue to use metallic plates for covering extensive defects in the frontal bone above the level of the sinus.

When swelling and tenderness have developed after an apparently successful plating, treatment by aspiration and penicillin have occasionally been followed by subsidence of infection when the organism has been penicillin sensitive and there has been no other predisposing factor such as slipping of the plate, inadequate circulation of the scalp, or communication with the frontal sinus. In the presence of a granulating sinus with exposure of the underlying plate, it is usually best to sacrifice the plate without delay, although in 26 cases of this series chemotherapy and plastic procedures have been followed by ultimate healing. I would recommend immediate removal



of any plate which is grossly infected or has underlying loose bone or metallic fragments to avoid the risk of infection penetrating the dura and serious risk to the patient or unnecessarily prolonged hospitalization. Time in hospital can be saved by taking out the plate and replacing it at a later date if so desired. In the case of small plates underlying fibrosis will often result in sufficient rigidity to make this unnecessary.

With the possible exception of repair of the brow ridge and defects in direct contact with the frontal sinus, I see no reason why we should return to the use of grafts of autogenous bone. Two deaths have followed the injudicious insertion of metallic plates in the stage of active infection, but no other fatal complications have been reported. Grafts of living bone are more difficult to insert and the cosmetic result after covering extensive defects is never as satisfactory. Reactivation of latent infection may also take place after their use. If even minor sepsis develops, the grafted bone will be lost, which has not been universally true of metallic plates. In addition these grafts occasionally soften and lose their shape after an apparently successful take (Ney<sup>2</sup>; Grant and Norcross<sup>17</sup>).

If alloplastic plates are to be used, what material is best? Experience at Newton D. Baker General Hospital (C. W. Elkins and T. Holbrook, personal communication) and my personal observations at the U. S. Naval Hospitals at Chelsea and St. Albans and the Veterans Administration Hospitals in New England have shown that tantalum, vitallium, and acrylic resin give rise to complications of the same order and frequency. Tantalum is by far the easiest to process and fit at the time of operation. I have preferred it for this reason to vitallium and lucite, which once cast can only be subjected to minor alterations. In epileptic subjects, however, the roentgen-ray translucent lucite plates should be used to permit subsequent study by air injection if the seizures continue.

It appears advisable not to attempt a primary repair after craniocerebral trauma, but to wait for at least two months if the wound heals by first intention. If there has been initial infection, plating should be deferred for at least six months, and longer in cases of infection with penicillin-resistant bacteria. Even greater conservatism should be used in cases where the first plate has had to be removed. In those extremely rare instances where infection has developed a second time, as well as in primary repair of defects involving the frontal sinus, the substitution of bone for metal should be considered. Thin grafts of cancellous bone taken from the iliac crest, recommended by Mowlem<sup>18</sup> and Carmody<sup>19</sup>, are especially well adapted for the repair of troublesome defects in the cranial vault. In all secondary cranioplasties it is extremely important that the overlying scalp be revised to eliminate areas of thin scar and deficient circulation. Leaks in the dura-arachnoid or communications with the frontal sinus must be searched for and closed; the plate, if reinserted, must be a perfect fit and fastened so

securely that it can never slip. All such operations should be followed by intensive use of both antibiotics and the sulfa compounds.

Insertion of metallic plates should be postponed for a long period in subjects who are likely to develop epilepsy. This complication, of course, most frequently occurs after deep wounds with dural penetration, indriven bony spicules or metallic fragments, and added sepsis. In these it is obvious that cranioplasty should be deferred because of the risk of reactivating infection. It would seem wise under these circumstances to wait at least a year and then to use roentgen ray transparent plates of acrylic resin, if there has been any history of seizures or evidence of an epileptogenic focus in the electroencephalogram. If this precaution is neglected, late epilepsy developing in the presence of a cerebral cicatrix and resistant to anticonvulsant drugs may necessitate removal of an otherwise satisfactory metallic plate in order to permit investigation of the cicatrix by pneumoencephalography.

#### CONCLUSIONS

The task of evaluating late complications following cranioplasty has been an interesting one. It is evident that a considerable number of alloplastic plates have led to complications (151 cases collected to date). The great majority of these have not been serious. Plastic closure of the defect in the scalp supplemented by chemotherapy in 35 cases and removal of the plate in the others has resulted in uncomplicated healing in 114. In four cases where plates were injudiciously inserted in septic fields infection spread through the meninges with cerebral abscess formation and death in 2 of the patients. Epilepsy has not resulted from the proper use of plates.

The majority of complications due to latent foci of infection have probably made themselves manifest by now, but a certain small number of patients with plates are liable to trouble as long as they live. This may follow trauma and laceration of the overlying scalp or infection from the underlying frontal sinus or mastoid. Under this circumstances grafts of living bone would presumably be tolerated better. Complications of this sort have been rare.

The most common complication after cranioplasty is infection or necrosis of the overlying scalp. This may occur after grafts of living bone as well as after insertion of plates of biologically inert metal or acrylic resin. In addition, grafts of bone may soften months or years after an apparently successful take. The causes of failure after plating and precautions necessary to prevent it have been discussed. The facts disclosed appear to justify the conclusion that a safe, simple, and satisfactory repair of a large cranial defect can be accomplished better and with no greater risk by an alloplastic plate than by grafts of cartilage or bone. When the cranial defect involves the frontal sinus, however, a return to the use of grafts of living bone is recommended.

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DR. WILDER PENFIELD, Montreal: I think Dr. White has done well to call attention to the necessity of observing surgical principles in the handling of plates and foreign bodies. It is necessary to be particularly careful of the ordinary surgical principles when dealing with a foreign body. One must be quite sure that the danger of infection is passed, that the circulation of the scalp and underlying dura is adequate. In our experience we have felt it better to close the dura, not to use any foreign body to fill in the dural defect, but to make sure that there is as nearly as possible complete closure of the dura so that there will be no connection between the spinal fluid and the plate. It is true that plates do not produce post-traumatic epilepsy so far as one can tell, and yet we have seen a good many patients in whom post-traumatic seizures began very shortly after insertion of a plate which was put in, often for reasons that are difficult to determine. When a man is getting along quite well with a little hole in his skull, he or his wife or someone wants it closed. I think we should be quite strong against such closure unless there is good purpose in it. I feel

that the use of tantalum plates is a real step forward provided proper principles are observed.

Another use for which we have found tantalum satisfactory is the following: We cut small disks not bigger than a button to go into the trephine or burr holes. That prevents eventual absorption and avoids excavation which otherwise appears in the scalp. Such indentations in the bald scalp of a friend, I have found very embarrassing. When bone disks or chips are used the telltale excavation always appears. Tantalum disks avoid that. The smaller the foreign body the less likely it is to give rise to trouble. I have seen many of these plates inserted that were much larger than need be. If the size is minimum the subsequent complications are reduced to a minimum.

DR. HOWARD NAFFZIGER, San Francisco: This presentation of Dr. White's includes a good many of the points stressed by our President in his address. Tantalum plates have a place, but I think they do not have as many places as are found for them. A good deal of the work in Veterans Hospitals in the neurosurgical line has had to do with removal of these plates as well as removal of the tantalum material placed about peripheral nerve suture lines.

In connection with the last point Dr. Penfield mentioned I would like to suggest that for small defects the use of mesh screen of tantalum or stainless steel is useful. This need be not much larger than a postage stamp, perhaps twice the size. There is a minimum of foreign material, the soft tissues grow through, and the cosmetic effect is good. As good, I believe, as with solid material. It can be shaped with scissors at the table and be put in in a moment. We have used this for several years to cover small defects that would otherwise be visible.

DR. GILBERT HORRAX, Boston (closing): I want to thank Dr. Penfield and Dr. Naffziger for discussing this paper, and I agree with them both in the things they have brought out. I was brought up in a school which did not believe in cranioplasty of any kind. I saw Dr. Cushing put in only one metal plate in 20 years and I think, as a matter of fact, that that had to come out. Any defects which were apparently conspicuous we occasionally filled in with bone. Bone does not make as neat and as nice a covering as tantalum, however, and I think in cases such as those mentioned by Dr. Penfield and Dr. Naffziger there is a definite place for this type of material, because it does make a very perfect contour of the skull such as it is impossible to get with any type of bony material.

# THE CLINICAL ASPECTS OF CHRONIC THYROIDITIS\*

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CHRONIC THYROIDITIS is not a rare disease, although any one surgeon may see few cases. Our excuse for reviewing the clinical aspects stems from our very low percentage of correct preoperative diagnosis, and the fact that we at times failed to recognize the pathology even when exposed at operation. We believe that chronic thyroiditis is *not* to be classed as a pathological curiosity, that it is an important matter from the clinical standpoint, and that it is most important for the patient that the situation is fully recognized at operation. Surgical sins, in this connection, are usually those of commission rather than omission, that is, too much is done. We were anxious that our Interns and Resident group be made well aware of this condition, and that our Attending Staff should aim at a higher percentage of correct preoperative diagnosis. We therefore reviewed 34 case records of thyroiditis from the Surgical Service at Roosevelt Hospital, and would like to present a few brief observations in regard to them.

We are not concerned with acute thyroiditis, (with or without suppuration), nor with specific infections such as syphilis, tuberculosis, actinomycosis, etc., but only with the obscure so-called "non-specific" chronic thyroiditis. Many excellent reviews of this general group are to be found, but nearly all deal largely with histopathology and etiology<sup>16, 17, 20</sup>. Most cases fall readily into three subgroups: (1) The struma lymphomatosa of Hashimoto<sup>12</sup> (occurring about once in every hundred routine thyroid operations). (2) The struma fibrosa, described by Riedel<sup>19</sup> more than 50 years ago (somewhat less common than the first group), and (3) the rarer giant cell type of De Quervain<sup>18</sup>. Much argument has been advanced to the effect that all these represent different phases of the same process, but the facts do not support this view and it seems to us that the division is clinically sound and useful. We have omitted the eight cases of acute thyroiditis (two with suppuration) from our group for this study, and also two cases in which the lymphoid changes in the gland were marked but still focal, leaving only 24 cases of undoubted chronic non-specific thyroiditis for detailed appraisal. We would like to offer a brief review of the features of each of the three groups.

For a complete picture of Hashimoto's disease one should read Joll's superb Hunterian lecture on the subject<sup>14</sup>. The condition is characterized by a diffuse lymphocytic involvement of the thyroid gland, with germinal centers, and widespread destruction of the thyroid cells. (One sees *focal* lymph-

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\* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

phoid accumulations in many cases of Graves disease, and in other thyroid conditions, but careful study easily differentiates these glands from the Hashimoto group.) Hashimoto's disease is extremely rare in males, and occurs chiefly in women at or near the menopause. It seems to be a degenerative process, rather than inflammatory. Adhesion to surrounding structures does not occur. The thyroid is usually diffusely enlarged, and the patient has some discomfort and a sense of "fullness." Pressure symptoms are mild. There is apt to be early myxoedema, although it is likely that, in the very early stages, there may be a transient hyperthyroidism. The thyroid, in Hashimoto's disease, is firm but not hard, is grayish pink in color, and finely lobulated, but does not contain distinct nodules. Its cut surface is yellowish. Among our 11 patients with the Hashimoto type of thyroiditis the usual story was that of slight discomfort, often intermittent, and usually more definite on one side than the other. In some the glands were quite large; in nearly all they were larger than normal; but in one case the size was within normal limits. We often felt sure, before operation, that one or both lobes were nodular, but the findings at operation revealed true nodularity in only one case. The lobes often resembled very large lymph nodes. The blood supply was usually less than normal. In one case, presenting a large diffuse struma lymphomatosa, lymphosarcoma followed partial resection after several months. Even in retrospect, the original sections were puzzling. This sequence is very rare, but has been reported by others<sup>14</sup>.

After a positive diagnosis, roentgen-ray therapy may be given with good results. Our own practice has been a symmetrical conservative type of resection. Extensive resection is unnecessary and unwise. In any event thyroid feeding will probably be needed.

Riedel's disease, or struma fibrosa, occurs in both sexes, but predominantly in women. It seems to be inflammatory in origin and the process spreads over the gland like a slow fire. The uninvolved portion of the thyroid is apt to be normal, and fairly normal thyroid function is thus preserved. The involved portion is pale and stony hard, presenting dense masses of fibrous tissue, and it is usually very adherent to the surrounding structures. This feature causes the trouble and the story is one of constriction. Freeing of the trachea, by tedious and careful excision of the isthmus, is often indicated — no more need be done, but the condition is often confused with malignancy and unwise and harmful surgery may follow. In Riedel's original case a false impression of malignancy was gathered. He attempted total extirpation but soon abandoned the idea due to technical difficulties, and was amazed that the patient continued to live and prosper. One of the early patients in our own series did not fare so well, for the impression of malignancy led to a total extirpation, with permanent loss of recurrent nerve and parathyroid function. If the frozen section diagnosis is doubtful, one should wait for permanent sections before further surgical removal is undertaken.

The rarer type of thyroiditis, the giant-cell type of De Quervain<sup>18</sup>, also appears to be of inflammatory origin. The patient is likely to have real pain. Involvement of the thyroid is limited to certain areas and there is some tendency to adherence to surrounding structures. The gland is *not* stony hard as in the Riedel type. The nature of the giant cells has been a matter of much dispute<sup>7, 8</sup>. The picture may closely simulate tuberculosis and has been

FIG 1.



FIG 2

FIG 1—Two types of Riedel's disease, from Joll's book *Diseases of The Thyroid Gland*: On the left, adherent muscle, and thyroid tissue "choked" by dense whorls of hard white fibrosis. On the right, the gradual slow progression of the process, with normal thyroid remaining at the lower pole.

FIG. 2—Gross specimen of lobes from our Case 1. The picture, both gross and microscopic, was typical of Hashimoto's disease. Several months later the remnants began to grow rapidly, having become lymphosarcoma.

called "pseudotuberculous thyroiditis." In the two cases of this sort in our series the pathology was confined to the right lower portion of the thyroid gland. It caused considerable discomfort with tracheal irritation. In one the frozen section diagnosis was neoplasm. Only a conservative resection was done and the permanent sections indicated the proper classification. She has remained well for more than 13 years. Recent reports indicate that roentgen-ray therapy, following a positive diagnosis may be the treatment of choice in this type<sup>5</sup>.

#### CHRONIC NON-SPECIFIC THYROIDITIS

##### CASE HISTORIES

**Case 1.**—A. S.: A 30-year-old white female entered the hospital, with presenting symptoms of diffuse swelling of the anterior neck, difficulty in respiration, and some pain of one month's duration. Physical examination showed marked symmetrical enlargement of the thyroid gland without fixation to the surrounding



FIG. 3.—Section from Case 1, showing what we thought to be an extensive Hashimoto type thyroiditis. The thyroid remnants soon became lymphosarcoma.

structures. There was no evidence of toxicity. BMR was normal. Preoperative diagnosis was diffuse non-toxic goiter. Treatment was subtotal thyroidectomy leaving large remnants. The postoperative diagnosis was Hashimoto's struma. This diagnosis was made by three different competent pathologists. (Fig. 2, 3.) Within a few months this patient died in another hospital of generalized lymphosarcoma, known to involve the thyroid gland, the neck, the mediastinum and abdomen.

**Case 2.**—M. L.: A 50-year-old white female entered the hospital with the presenting symptoms of pain and fullness in the right anterior neck, of 18 months' duration. Physical examination revealed a firm, tender nodule in the right lobe of the thyroid gland. The patient had been suffering from low grade hypothyroidism and had a BMR of minus 9. The clinical diagnosis was thyroiditis. The operation was partial thyroidectomy, of a conservative type. The postoperative



diagnosis was Riedel's struma. The patient has been well since the operation and has no complaints.

**Case 3.—J. D.:** A 50-year-old white female entered the hospital with the presenting symptoms of enlargement of the right side of the thyroid, associated with pain of about 14 months' duration. Physical examination revealed a gland which was rather firm. The BMR was plus 9. The preoperative diagnosis was diffuse goiter, questionably toxic. The operation was subtotal thyroidectomy. Postoperative diagnosis was Riedel's struma. (This patient had had a mastectomy in Warsaw in 1939 for carcinoma of the breast.)

**Case 4.—D.M.:** A 53-year-old white female entered the hospital with the presenting complaint of a lump in the lower anterior neck of one year's duration. Physical examination revealed a firm, symmetrical, smooth thyroid gland about twice normal size. This patient had slight lidlag and the left eye was weak in convergence. The preoperative diagnosis was diffuse, mildly toxic goiter. Treatment was subtotal thyroidectomy. It is interesting to note that the thyroid gland extended most of the way around the trachea and the gland tissue removed weighed 108 Gm. In spite of this the patient had no symptoms of pressure. The postoperative diagnosis was Hashimoto's struma. (Fig. 4.)

**Case 5.—N. S.:** A 62-year-old white female entered the hospital with the chief complaint of a mass in her neck of about two months' duration. Physical examination revealed a firm, ovoid mass in the left side of the neck which was not tender. This patient had been suffering from chronic sinusitis for many years. The preoperative diagnosis was non-toxic nodular goiter. Treatment was excision of a firm nodular area in the lower pole of the left lobe of the thyroid gland. Postoperative diagnosis was Hashimoto's struma. The patient has been well since her operation with no complaints referable to the thyroid gland.

**Case 6.—I. D.:** A 51-year-old white female entered the hospital with the following complaints; swelling in the neck and pressure in the back of the throat of eight weeks' duration. Physical examination revealed a firm swelling in the right lobe of the thyroid. The BMR was minus 21. Preoperative diagnosis was non-toxic nodular goiter. The treatment was subtotal thyroidectomy, with the removal of only a small amount of each lobe. The postoperative diagnosis was Hashimoto's struma. Since the operation the patient has been taking thyroid extract, grains  $1\frac{1}{2}$  every day, and has continued to be somewhat unstable emotionally, as she was preoperatively. A BMR repeated six months after operation was minus 28.

**Case 7.—M. S.:** A 52-year-old white graduate nurse entered the hospital with the chief complaint of swelling in the anterior neck, particularly on the left, associated with difficulty in swallowing, of four days' duration, plus some hoarseness for the same period of time. Physical examination revealed an enlargement of the left lobe of the thyroid with some definite tenderness. The BMR was minus 11. The diagnosis at this time was acute thyroiditis and tonsillitis. The patient was treated with warm saline gargles and penicillin but this did not give complete relief of the thyroid symptoms. Because of the persistence of the swelling and the difficulty in swallowing, a left subtotal hemithyroidectomy, including the isthmus, was done. At operation it appeared that the trachea was shifted to the right and the left lobe was enlarged and yellowish-pink in color. The diagnosis of Hashimoto's struma was made at operation. It is interesting to note that this patient had been bothered for a good many months with chronic tonsillitis and that about six months prior to this current hospital admission she had had a similar bout of swelling in the region of the thyroid. After leaving the hospital the patient did very well. Her BMR was minus 14 twenty months after operation. She has no clinical signs of hypothyroidism in spite of the lowered basal

metabolism. She has worked steadily except for a few weeks following an operation for gallstones.

**Case 8.**—M. G.: A 35-year-old female entered the hospital with the presenting complaints of nervousness, slight pain and swelling in the anterior neck, particularly on the right, of about six months' duration. This patient also had mild difficulty in swallowing and slight difficulty in breathing during exertion. Physical examina-

FIG. 4.

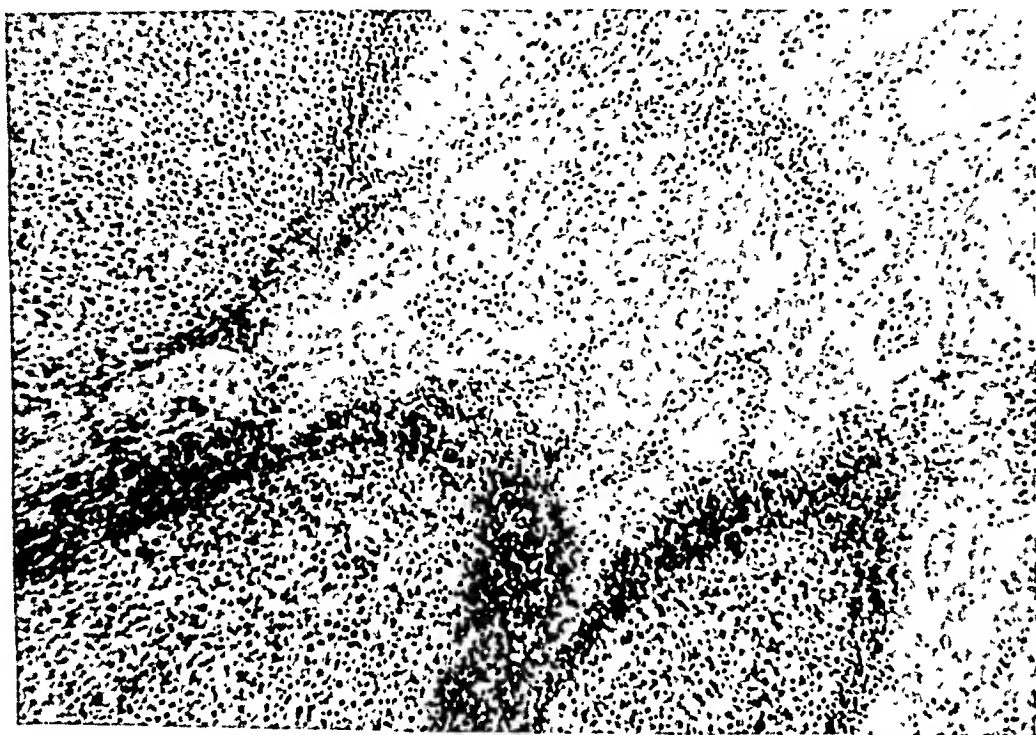


FIG. 5.

FIG. 4.—Case 4. Section showing large germinal centers, and infiltration of remaining areas of thyroid tissue in Hashimoto's struma.

FIG. 5.—Case 16. Typical section showing Hashimoto type thyroiditis. It is easy to see why these patients all tend toward myxoedema.

tion revealed moderate enlargement of the right lobe of the thyroid gland. This area was slightly tender and firm. The patient had slight tremor of the hands and the pulse was 100. The BMR was plus 9. The preoperative diagnosis was low grade toxic nodular goiter or possibly thyroiditis. During the operation the thyroid looked as if it were involved in a malignancy or a Riedel's struma. The gland was whitish-yellow in color and rather firm. The right lobe of the gland was very hard. A right partial thyroidectomy including the isthmus was done. A frozen section at operation showed Riedel's struma and so it was decided to leave the left lobe in situ. The left lobe was freed from the trachea. Postoperative diagnosis was Riedel's struma. Since operation the patient has felt fine but has had to take about 2 grains of thyroid extract every day. BMR since operation has varied from minus 7 to minus 20.

**Case 9.—E. H.:** A 56-year-old white female entered the hospital with the following complaints: lump in the right thyroid lobe, nervousness, weight loss and occasional tenderness in the right lobe of the thyroid for about 6 months. Physical examination revealed a diffusely enlarged right lobe of the thyroid with a hard nodule in the region of the isthmus. The entire gland was quite firm. BMR was plus 2. A preoperative diagnosis was nodular, non-toxic goiter, with other choices of malignancy and Riedel's struma. The treatment was conservative bilateral partial thyroidectomy. At operation the gland was pale, firm and rather avascular in appearance. It was yellowish-gray in cross section with islands of what appeared to be normal thyroid tissue. Postoperative diagnosis was Riedel's struma. The BMR 6 years after operation was minus 27. The patient feels somewhat tired but has no other definite symptoms of hypothyroidism. The patient has been advised to take thyroid extract but has refused to do this.

**Case 10.—E. L.:** A 21-year-old female entered the hospital with the following complaints: a lump in the neck of five months' duration, pain in the neck of two months' duration, laryngeal stridor, dysphagia, cough, hoarseness and chronic pharyngitis of seven weeks' duration. This patient had had osteomyelitis of the jaw one and one-half years ago. This patient had been treated in another hospital seven weeks prior to entry here. The treatment in the other hospital was directed towards her pharyngitis. BMR on admission here was minus 19. The preoperative diagnosis was Riedel's struma. Treatment was division of the isthmus of the thyroid with removal of the isthmus and a wedge of each lobe of the thyroid gland. The gland was adherent to the surrounding tissues and frozen to the trachea. This patient's preoperative tracheal constriction was so severe that a tracheotomy was considered at the time of operation.

**Case 11.—K. S.:** A 20-year-old white female entered the hospital with the following complaints: diffuse swelling of the anterior neck, and slight prominence of the eyes of several months' duration and menorrhagia of five years' duration. Physical examination revealed bilateral firm enlargement of the thyroid gland to three times normal size. The BMR was plus 13. The treatment was subtotal thyroidectomy. Preoperative diagnosis was diffuse toxic goiter of mild degree. Postoperative diagnosis was Riedel's struma with some areas of moderate hyperplasia of the gland.

**Case 12.—H. W.:** A 43-year-old white female entered the hospital complaining of intermittent hoarseness and choking associated with painful swelling in the left side of the neck anteriorly. There was also discomfort in swallowing. Physical examination revealed moderate enlargement and irregularity in shape and consistency of the thyroid gland. The left lobe was larger than the right and there were some dilated veins over the anterior neck. The BMR was minus 10. Preoperative diagnosis was non-toxic nodular goiter. Treatment was left subtotal thyroidectomy with removal of the isthmus. Postoperative diagnosis was Hashi-

moto's struma. Since operation the patient has had occasional discomfort in the neck, but no evidence of hypothyroidism and no thyroid extract has been required.

**Case 13.—E. M.:** A 47-year-old white female entered the hospital with the chief complaint of a lump in the thyroid region, some hoarseness necessitating the frequent clearing of the throat, irregular menses of four years' duration, weight loss and slight increase in nervousness. All of this was of two years' duration except the prolonged irregular menses. Physical examination revealed diffuse enlargement of the thyroid gland, most marked in the region of the isthmus. The BMR was minus 13 preoperatively. The preoperative diagnosis was non-toxic nodular goiter. Treatment was total thyroidectomy with tracheotomy. It is interesting to note that the operator believed he was dealing with an extensive thyroid carcinoma. In cross section the gland was grayish-white, and contained hard nodular areas. The right lobe was quite adherent to the trachea and surrounding muscle. The frozen section at the time of operation seemed to indicate a carcinoma of the thyroid. Upon leaving the hospital the patient had a complete left cord paralysis and a slightly paralyzed right cord. The final pathological diagnosis was Riedel's struma.

**Case 14.—A. H.:** A 49-year-old white female entered the hospital with the chief complaint of a pulsating mass in the right neck of six-years' duration. Physical examination revealed a diffuse enlargement of the thyroid gland most marked on the right. BMR was minus 14. Treatment was subtotal thyroidectomy. At operation a large nodule of the right lobe of the thyroid gland seemed to move with each pulsation of an underlying atypical carotid artery. The artery was not dilated. The postoperative diagnosis was Hashimoto's struma in an involuted nodular thyroid gland. After leaving the hospital the patient had no complaints and has not needed any thyroid extract. Her BMR was plus 1 seven months postoperatively.

**Case 15.—A. T.:** A 40-year-old white female entered the hospital complaining of a mass in the thyroid of 20 years' duration, with a slight increase in its size in the last few months. Physical examination revealed a rounded firm enlargement of the right lobe of the thyroid. The gland was freely movable. Preoperative diagnosis was thyroiditis, a first choice because of the firmness and tenderness of the thyroid gland, with neoplasm as second choice. Treatment was right partial thyroidectomy, and release of the left lobe of the thyroid from the trachea. Postoperative diagnosis was Hashimoto's struma. (Fig. 5.) After leaving the hospital the patient has had very low grade hypothyroidism. She is otherwise well.

**Case 16.—S. T.:** A 45-year-old-white female entered the hospital with the following complaints: lump in the anterior neck of one year's duration, fatigue and dyspnea of two years' duration, dysphagia of one year's duration. Physical examination revealed a rather diffusely enlarged thyroid gland most pronounced on the right behind and below the clavicle. BMR was minus 27. Preoperative diagnosis was adenoma of thyroid. Treatment was right subtotal thyroidectomy. Postoperative diagnosis was Hashimoto's struma.

**Case 17.—A. T.:** A 71-year-old white female entered the hospital with the following complaints: constant irritation of the throat with constant desire to clear it, cough, fullness in the anterior neck and variation in the size of the swelling of six months' duration. Physical examination revealed firm areas in the right lobe and isthmus which were not very mobile. Preoperative diagnosis was first, carcinoma of the thyroid, and second Riedel's struma. Treatment was right partial thyroidectomy with removal of a wedge of tissue from the left lobe and freeing of the left lobe from the trachea. The lower pole of the right lobe was adherent to the trachea in the region of the right recurrent laryngeal nerve. Postoperative diagnosis was chronic thyroiditis of the DeQuervain type. Since leaving

the hospital the patient has been well except for a long standing high blood pressure. She has been followed for 14 years since operation.

**Case 18.**—B. S.: A 50-year-old white female entered the hospital with the complaint of swelling and pain in the thyroid region. The patient had lost 20 pounds weight, was nervous and perspired a great deal. She had also had amenorrhea for the past six months and other associated menopausal symptoms. BMR preoperatively was plus 11. Preoperative diagnosis was mildly toxic nodular goiter, or carcinoma of the thyroid. Treatment was right partial thyroidectomy. At operation the right lobe was very hard and yellow but not adherent. Because of the large giant cells and the similarity to the picture of tuberculosis, the pathologist was prompted to do several sections and stained them for bacilli but none were found. (Fig. 6.) The postoperative diagnosis was chronic thyroiditis of the DeQuervain type.

**Case 19.**—C. W.: A 73-year-old white female entered the hospital with the chief complaint of a "lump" in the neck of two months' duration. Physical exami-

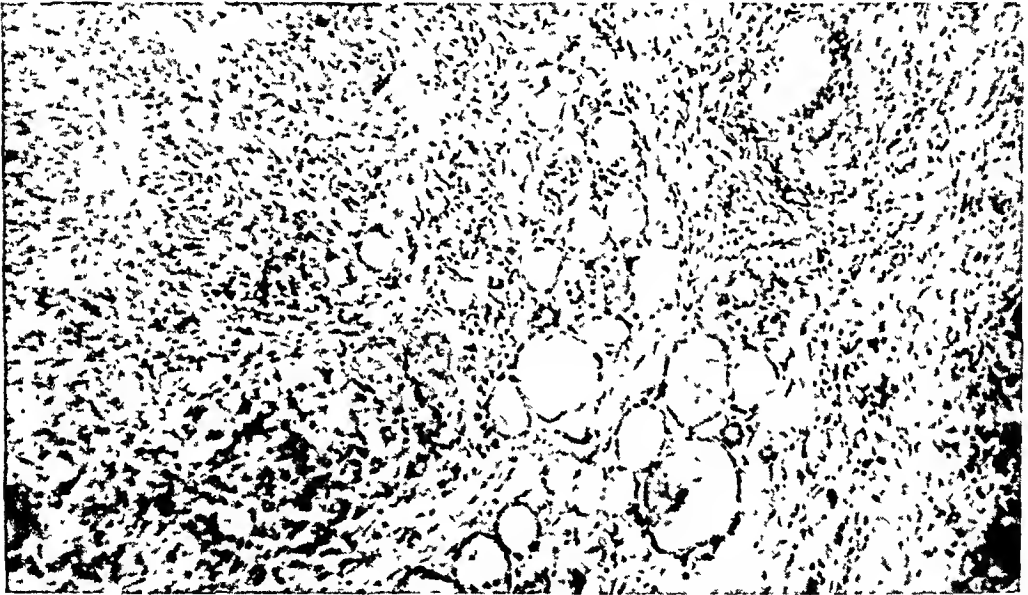


FIG. 6.—Section from Case 18, near the advancing edge of the process. Riedel's disease closely resembles this type, but it really belongs in the "giant-cell" or "Pseudo-tuberculous" thyroiditis group.

nation showed two firm areas in the thyroid gland. BMR was plus 7. The patient had had an upper respiratory infection and had it at the time of entry. Preoperative diagnosis was non-toxic nodular goiter. Treatment was subtotal thyroidectomy. At operation the gland was very hard, nodular and gray. Frozen section was done at this time because the gland looked as if it might be the seat of a primary neoplasm. This patient had had a history of intermittent cervical adenitis of many months' duration prior to this hospital entry. Postoperative diagnosis was Riedel's struma. BMR preoperatively was plus 7. Two months' postoperatively it was minus 17 and the patient was taking one grain of thyroid extract every day, but had no obvious symptoms of hypothyroidism.

**Case 20.**—C. F.: A 21-year-old white female entered the hospital with the chief complaint of a painful mass in the anterior neck of one year's duration. Physical examination revealed a firm swelling of the thyroid gland most marked on the right. The patient had allegedly lost 20 pounds. BMR was minus 18. Pre-

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operative diagnosis was non-toxic nodular goiter. Operation was subtotal thyroidectomy in two stages. Both stages were very conservative. BMR after the second operation was minus 25. In the interval between the first and second operation the left lobe of the thyroid had increased considerably in size. Post-operative diagnosis was Hashimoto's struma. Since leaving the hospital the patient has been well and has taken a half grain of thyroid occasionally when she feels tired. There is no real picture of hypothyroidism.

Case 21.—R. D.: A 48-year-old female entered the hospital with the chief complaint of swelling in the neck of five months' duration following extraction

FIG. 7.

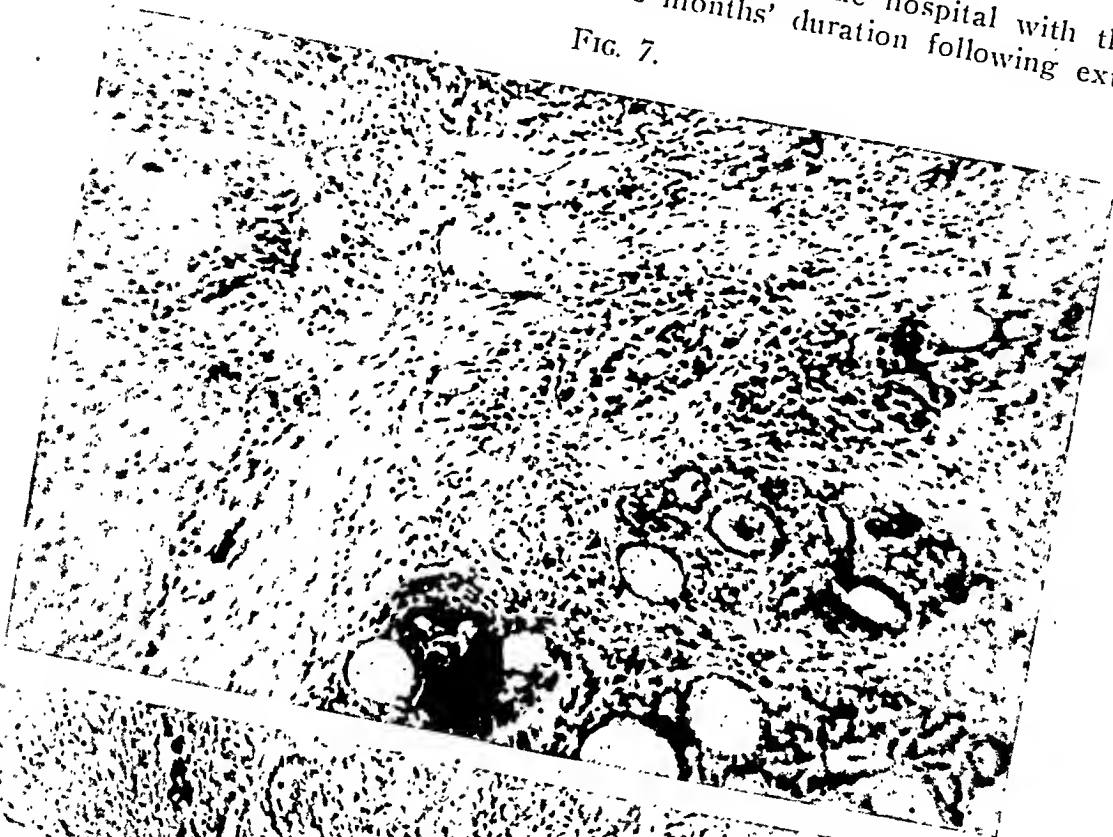


FIG. 8.

FIG. 7.—Section from Case 21. Reidel type chronic thyroiditis.  
FIG. 8.—Section from Case 23. Reidel type showing advanced replacement of thyroid acini by dense fibrous strands.

of teeth. The patient allegedly lost 31 pounds. She was nervous, complained of pressure symptoms in the neck and had a temperature of 101 on entry into the hospital. Physical examination revealed a diffusely enlarged, irregular, hard thyroid gland. A preoperative BMR was minus 6. Preoperative diagnosis was non-toxic nodular goiter or a possible malignancy. Treatment was subtotal thyroidectomy. The specimen was gritty hard in appearance. (Fig. 7.) Postoperatively BMR was plus 1. Postoperative diagnosis was Riedel's struma.

**Case 22.—C. M.:** A 32-year-old white female entered the hospital with the chief complaint of a painful and marked swelling of the anterior neck of three weeks' duration. The patient was also nervous, had a tremor and had allegedly lost 49 pounds. Physical examination revealed a firm, tender, enlarged thyroid gland. BMR was plus 33 on one occasion and plus 29 on another. Preoperative diagnosis was diffuse toxic goiter or possibly thyroiditis. Treatment was a wedge shaped removal of a piece of each lobe plus dissection of the isthmus. Postoperative diagnosis was Riedel's struma.

**Case 23.—M. N.:** A 47-year-old white female entered the hospital with the chief complaint of an enlarged thyroid of 12 years' duration with a two months' story of a rather sudden increase in the size. Physical examination revealed an enlarged, rather irregular thyroid, particularly on the right. There was no apparent pain. BMR was minus 5. Preoperative diagnosis was non-toxic nodular goiter. The operation was biopsy of the right lobe and excision of the isthmus plus a wedge-shaped excision of each lobe in the region of the trachea. (Fig. 8.) At operation, the muscles were very adherent to the gland. The trachea was freed with difficulty. Postoperative diagnosis was Riedel's struma. Since operation the patient has been well and she has had no complaints, and no evidence of hypothyroidism.

**Case 24.—L. D.:** A 35-year-old white female entered the hospital complaining of fatigue and enlargement of the thyroid gland, particularly on the right. Physical examination revealed an enlarged, firm gland. Treatment was subtotal thyroidectomy. Preoperative diagnosis was diffuse, mildly toxic goiter. Postoperative diagnosis was Hashimoto's struma, with a few areas of slightly hyperplastic thyroid tissue.

#### SUMMARY OF THE CLINICAL ASPECTS OF 24 CASES OF CHRONIC NON-SPECIFIC THYROIDITIS

In 24 proven cases of chronic thyroiditis there were 11 cases of Hashimoto's struma, 1 of which became lymphosarcoma, 11 cases of Riedel's struma and 2 cases of pseudotuberculous thyroiditis of DeQuervain (giant cell type). The average age of the Hashimoto's cases was 43.8 years, of the Riedel's cases 44.2 years and the DeQuervain cases 61 years. All these cases were white women. 10 of the 11 cases of Hashimoto's struma (91%) showed enlargement of the gland, and all cases of the Riedel's and DeQuervain types showed enlargement of the gland. Pain or tenderness in the thyroid gland occurred in 7 of the 11 (64%) of the Riedel cases, 5 of the 11 (45%) of the Hashimoto cases and 1 of the 2 (50%) of the DeQuervain cases. Pressure symptoms such as hoarseness, dysphagia, dyspnea or choking occurred in 6 of 11 (55%) of the Hashimoto cases, in 5 of the 11 (45%) of the Riedel's cases and 1 of the 2 (50%) of the DeQuervain cases. The duration of symptoms in the Riedel group averaged 8 months,



in the Hashimoto group 5 months and in the DeQuervain group 6 months. One patient died, a mortality of 4.2%. This patient died of lymphosarcoma which involved the thyroid gland, mediastinum, etc. This patient's original diagnosis was Hashimoto's struma. The correct clinical diagnosis was made in 3 of 11 (28%) of both the Hashimoto's and Riedel's groups and in neither case of the DeQuervain type. The diagnosis of malignancy of the thyroid gland preoperatively or at operation before the pathological report was available occurred in 6 of the 11 (55%) cases of the Riedel's group, 1 of the 11 cases (9%) of the Hashimoto's group and in 2 of the 2 cases (100%) of the DeQuervain group.

#### SUMMARY AND CONCLUSIONS

Thirty-four case records of "thyroiditis" have been reviewed from the surgical service at Roosevelt Hospital. Deletion of the acute cases, and of 2 in which the pathology was rather limited, left 24 cases of undoubted "non-specific chronic thyroiditis" for detailed study. Eleven were of the Hashimoto type (struma lymphomatosa), 11 of the Riedel type (struma fibrosa), and 2 of the giant-cell type of DeQuervain.

One factor in the amazingly low percentage of correct preoperative diagnosis in these conditions, in most hospitals, is that chronic thyroiditis is often not even mentioned as a possibility.

Even when the thyroid is exposed at the operating table, a false impression is often gained, and this may lead to unnecessary and harmful surgery.

A plea is made for the recognition of chronic thyroiditis before operation, and at operation. It is highly important for the patients that we do so.

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DR. SAMUEL F. MARSHALL, Boston: I want to commend Dr. Patterson for the very clear clinical picture of thyroiditis. As he has stated, the disease is not common but neither is it rare, because we do see it frequently and, if we are aware of the pathologic process in the thyroid gland, I am sure we can diagnose it from a clinical standpoint many times. We have been interested in this problem, and Dr. William Meisner of Dr. Shields Warren's pathology service and myself went over our material in the Lahey Clinic, and re-examined all the tissue removed. We found, in approximately 25,000 thyroid operations, about 187 cases of thyroiditis, proven by pathologic examination. The picture is quite characteristic. As you know, the thyroid gland will react to trauma and irritation in a quite characteristic manner. The reaction, of course, may be due to irritation or to trauma, and may result in stromal changes or in epithelial changes, so that we were able to divide the 187 cases into three groups.

The first group is the infectious group in which Riedel's struma is the end stage of infection. The second group, Hashimoto's struma, struma lymphomatosa and, finally, the third group we called the non-specific group because we were not able to get sufficient characteristics to permit a more definite classification. The reaction, as I said, may be epithelial or may be stromal, and it is not uncommon to see the foreign body giant cell reaction, which is probably due to colloid spillage in this stromal tissue. We believe that the diagnosis can be established, however, in the greater percentage of cases, and we have had many more cases in which a clinical diagnosis could be made. I am not prepared to say what the number is, but it must be at least two or three times the number that were operated upon and, too, the diagnosis was faulty in that operative group, but that is easy to see inasmuch as they were operated upon because we could not definitely rule out malignancy. In 187 cases that came to surgery, in only 44 was the correct diagnosis made.

The matter of treatment is of some concern; most cases do not require surgery. If the diagnosis is established and the patient can be followed over a long period, operation is unnecessary except to rule out malignancy and to decompress the trachea because of the pressure which occurs sometimes. Dr. Lahey has described the method of removal of the thyroid isthmus over the trachea and suture of the pre-thyroid muscles to the trachea to prevent this vise-like pressure from again occurring on the trachea.

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There is one point of value in surgical care of these cases. We must remember that in the infectious group, of the type that is called Riedel's in its end stages, we rarely see myxedema. We found myxedema in about 27 per cent of the cases, but in the advanced stage myxedema was present in 57 per cent. So it is important not to do a subtotal thyroidectomy on these cases, both from the standpoint of reducing the secretory epithelium and from the standpoint of the technical problems that are apt to follow attempts at removal of this very adherent gland. On the other hand, Hashimoto's can be depressed much more easily by radical removal of the gland, because practically all these cases get myxedema whether you operate upon them or not. This has been reported in other studies and was also our experience—80 per cent of our cases had myxedema. In the other group, the non-specific group, we should also avoid operation, and we noted 30 per cent myxedema in those cases. We have not used x-ray therapy, nor do we care to do so, because we want to preserve the secretory epithelium wherever possible; furthermore we want to establish the diagnosis and, again, x-ray therapy may produce more scarring and more fibrosis and make operative approach extremely difficult.

DR. F. A. BOTHE, Philadelphia: My attention has been attracted to the different colors that the types of chronic thyroiditis exhibit at the operating table. Cognizant of this fact, when we approach a very firm gland, careful hemostasis should be used so we may observe the gland's true color. My experience is confined to only 17 cases, but we have noted that the gland is a definite purplish-gray color in Hashimoto's disease, whereas it is yellowish-red in Riedel's struma. In Hashimoto's disease we have found lobulation of the gland and, in several instances, this was so pronounced that it appeared as though several lymph nodes were attached to its surface. This lobulation has not been seen in cases of Riedel's struma.

Ewing has made contribution to our knowledge of chronic thyroiditis. However, the work Graham reported in 1931 cleared up our previous misconception of thyroiditis and established struma lymphomatosa and Riedel's struma as separate and distinct types of chronic thyroiditis. Ewing believed that Riedel's struma was a later stage of Hashimoto's disease. Cases have been reported in which a second operation several years later has been performed upon patients with struma lymphomatosa and there was no change in the cellular structure of the gland from that found at the first operation; this is in keeping with Graham's viewpoint.

Lobectomy has been practiced routinely in the struma lymphomatosa cases to establish a diagnosis, rule out malignancy and to prevent subsequent tracheal obstruction. It is realized that obstructive complications are far more frequent in Riedel's struma.

One patient operated about 15 years ago has been followed very closely. A total thyroidectomy was performed, as it was impossible from a study of the frozen sections to distinguish the case from one of small round cell carcinoma. Six months later the patient developed hypoparathyroidism. Some previous writers have called attention to the fact that struma lymphomatosa may spread to the glands of internal secretion. It was felt that this complication was due to the surgical procedure; however, the fact that it did not develop until six months after operation led to the thought that this might be a case in which the disease spread to the parathyroid glands. In the past year, at the age of 82, the patient fell down two flights of stairs. She complained of severe pain in the hip and the foot on the affected side was everted. An x-ray of the hip was negative for fracture, but to our surprise the cortex of the femur had become greatly thickened even though the hypoparathyroidism had been symptomatically controlled by replacement therapy.

# THE RESULTS OF A SPECIFICALLY CO-ORDINATED PLAN OF MEDICAL AND SURGICAL TREATMENT OF ESSENTIAL HYPERTENSION\*

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IN 1934, BARKER AND DAVIS formulated a plan for the study of patients with essential hypertension for whom surgical therapy might be undertaken. In 1939, they reported<sup>1</sup> upon their clinical and experimental experiences and attempted to make clear for others the principles upon which their work was being carried out in the hope that eventually it would lend itself to comparison with that of other groups engaged in similar work.

In part, it was stated that:

*"clinically, the criteria for classifying patients as cases of essential hypertension vary considerably among various groups of workers. Yet, before surgical procedures can be evaluated, agreement must be reached as to exactly which type of patient is being operated upon, or should be operated upon."*

"There is agreement that the clinical course of a young adult with essential hypertension may be an intense progression to a fatal termination within two years; that is, uremia and death cannot be stayed by medical treatment. On the other hand, a variable hypertension of mild degree may exist in adults under 35 years of age, which represents vasomotor instability and either requires no treatment or is controlled by simple medical measures. Late in life, a high systolic blood pressure with a normal, or nearly normal diastolic pressure, related to sclerosis of the large vessels of the body is relatively unimportant and does not require treatment."

"About 90% of the mild cases of hypertension at all ages either have no symptoms or are easily relieved. Of the cases of moderately increased blood pressure, 75% either have no symptoms or can be relieved. Of the severe group of 45 years of age, many have reached a late stage in the disease after a long course. Under medical treatment, at least 30% of these patients may obtain a substantial fall in their blood pressure and another 40% may obtain symptomatic relief over long periods of time. The remaining 30% in this group have marked and irreversible vascular changes, which make amelioration of their symptoms impossible. We are confronted then with the group of young adults with malignant progression of their symptoms of hypertension and those patients with a moderate hypertension under 45 years of age for whom surgical intervention may hold hope."

"Malignant hypertension is denoted by that fulminating endothelial necrotic state which may develop at any time in any hypertensive patient which usually rushes him through to an early death with evidences of widespread destruction of the vessels in the kidneys, retinae and brain.

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\* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

Such changes may come on suddenly in patients with severe essential hypertension resulting in terrific headaches, stupor, motor phenomena, cardiac gallop rhythm, hemorrhages from the nose and urinary tract, and actual rupture of the retinal vessels. Such a fulminating episode may be as dramatic as a fatal lobar pneumonia. However, some of the malignant cases may go on for months with periods of exacerbation and remission. Rarely, such a patient may be much improved for a long time after a coronary occlusion or a cerebral vascular accident. We have also seen a reversal from the malignant to the essential type by reducing the blood pressure and controlling it by the administration of cyanates. *This type of reversal in the phases of the hypertensive state should cause us to consider carefully surgical treatment."*

"At which stage in the disease is surgery contraindicated and what constitutes the basic factors for such contraindications? Is it fair to require that the surgical treatment of essential hypertension be evaluated according to its effectiveness in various types and degrees of severity of the disease and the sole criterion be the effect upon the systolic blood pressure? If so, by what standards can the types and degree of severity of the disease be so classified that the results of surgical therapy in one clinic may be compared with another? One may suspect that many of the favorable surgical results reported might be duplicated by another group of workers through medical measures alone. Lowering of the diastolic pressure is a far more significant result relative to the patient's welfare than lowering of the systolic pressure. What train of physiological events results in lowering of the pressure following sympathectomy?"

We have adhered to these generally stated principles in the past 14 years and from a study of some 700 patients with essential hypertension have classified them according to therapeutic and clinical types. We do not expect complete agreement and acceptance of this classification, but it has seemed to us to be the most logical one based upon facts which can be definitely known about the patient, and to be a simple one which others can correlate with their own particular classification so that comparison of the results of surgical therapy can be made. Finally, we decided early to limit our surgical therapy to one of the types of essential hypertension and we chose that group for which medical treatment was inadequate, and progress of the disease appeared to be imminently fatal.

#### CLASSIFICATION OF HYPERTENSION

We believe that patients with essential hypertension can be divided clinically and therapeutically into five groups:

**GROUP I—*Fluctuant*:** This type represents a large proportion of the early cases of hypertension observed usually in the teens or early twenties, has often been described as adolescent hypertension, and is not associated with renal disease. It is asymptomatic and is only discovered as a result of a routine physical examination. During these early years it is impossible to tell whether the disease will remain quiescent, progress into one of the other clinical types, or in some cases disappear entirely.

As long as the etiology can not be determined, associated renal disease

is not discovered and the patient remains asymptomatic, it is questionable whether or not any therapy should be instituted. These patients uniformly respond well to thiocyanate; however, the patients are not co-operative because their early hypertension gives them so little trouble. The following case history is presented in order to show the effect of potassium thiocyanate on this type of hypertensive patient.

Case 1.—Mr. J. V., a 26-year-old white accountant, was first seen in the early part of 1947. At this time, he gave a history of asymptomatic hypertension for 5 years. He complained of nervousness and his general appearance was that of a normal person of Italian extraction. The fundi were of Grade 1 classification with only spasm and some streaking; the blood pressure was 160/100 mm. of Hg.: and no other physical abnormalities were present. Laboratory findings of the urine and blood were entirely normal and the electrocardiogram changes consisted of very minimal (less than 0.1

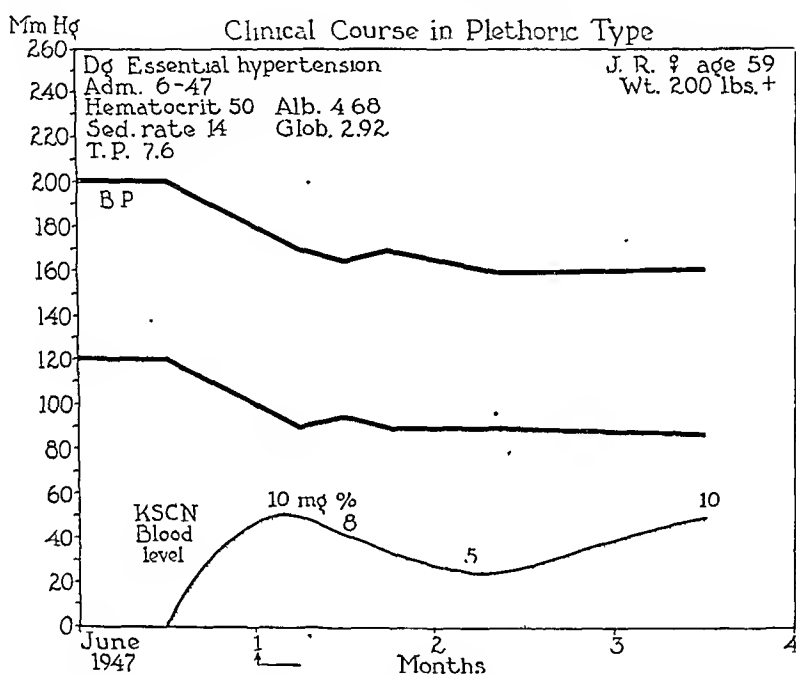


FIG. 1.—A graph showing the clinical course of a patient, the plethoric type of hypertension, showing the relationship between the blood pressure range and the blood thiocyanate level.

mm.) elevations of St segments 1 and 4. He was placed on thiocyanate therapy and in three weeks felt much more calm. His blood pressure gradually decreased until, on May 10th, it was within normal range.

On May 1, 1948, his blood pressure was 120/76 and he was taking three grains of potassium thiocyanate every other day and maintaining a blood thiocyanate level of 10 mg. per cent.

This case represents early vasospastic, or hormonal, hypertension and would probably respond best to surgical sympathectomy.

GROUP II—*Plethoric*: The plethoric hypertensive is usually a typical "businessman" with hypertension, who is energetic, active, overweight and may have distressing symptoms, particularly of headache, vertigo and angiod distress associated with a cardiovascular disturbance.

The hematocrit is usually found to be over 50% (red blood count over five million) and the sedimentation rate 1 to 5 mm. or less in one hour. We are in the habit of describing this blood as viscid or "sticky", and in such cases, cerebral or coronary thromboses are common.

Provided that the patients do not have associated irreversible renal disease, continued control of blood cyanate concentration will result in a rather prompt relief of the hypertensive symptoms and a gradual diminution in, first, the systolic, and later, the diastolic pressure. It is dangerous to drop these patients' pressures rapidly; therefore, the early dosage of the cyanates should be small and gradually increased as renal thiocyanate clearance improves. Often these patients have a rapid renal clearance of thiocyanate and may require as much as 20 gr. of the drug daily to maintain an adequate blood concentration.

During the first few months of treatment, the hematocrit will drop to 45 or less and the sedimentation rate will increase 10 or 15 mm. in an hour, which represents a definite change in the hemogram resulting from a thiocyanate effect on the red blood count and therefore on blood viscosity.

These patients represent the most favorable group for treatment with thiocyanates and can be best illustrated not only by the case history which follows, but also by a line graph (Fig. I) which illustrates the effect of thiocyanate on the blood pressure and hemogram in this type of individual.

**Case 2.**—Mr. J. R. a 59-year-old white man, was first seen in late June, 1947, complaining of shortness of breath on exertion, a buzzing in his head in the daytime and nocturia. He said that his blood pressure had been high as long as he could remember and that in 1946, he had had some heart failure and had been required to spend two months in bed. A laboratory survey showed a sedimentation rate 5; hematocrit 50; total protein 7.6; albumen 4.68; globulin 2.92; blood urea nitrogen 12.6; and uric acid, 5.2. The electrocardiogram demonstrated the presence of a first degree heart block.

On physical examination his fundi were of Class 2 severity, and aside from a plethoric stocky appearance and a blood pressure of 220/120, there were no significant findings.

He was placed on thiocyanate therapy and in two weeks he had a blood cyanate level of 10 associated with a fall of pressure to 170/90. Blood pressures and thiocyanate levels have been at this level or lower for ten months and the cardiogram shows a diminution in the PR interval of .02 and there is no deformity of a recent coronary occlusion. His sedimentation rate is now 15 mm. in one hour and the hematocrit is 47%. He has had no hypertensive symptoms since his blood pressure has dropped to the lower levels.

**GROUP III—Menopausal** hypertension is one of the most frequent types of hypertension seen in the female and corresponds in many respects to the plethoric type of hypertension in the male. It is usually accompanied by numerous and severe symptoms of hypertension which are superimposed upon those that are often associated with the menopause. Unlike the plethoric type of hypertension, however, a high hematocrit and low sedimentation rate are not often seen. The blood cholesterol is likely to be elevated.

The hypertensive, as well as the menopausal symptoms, can often be controlled by estrogenic therapy and sedation alone, but the blood pressure which is not affected by these measures will often respond to thiocyanate therapy.

By the above description we do not wish to infer that menopause in itself is a cause of essential hypertension. It most likely is not. However, menopause does exaggerate the symptoms of a pre-existing, or coincidental, hypertension in patients with only a moderate elevation of the blood pressure. There may be a wide fluctuation in the blood pressure readings in the level type, or a pre-existing diastolic fixed type of blood pressure may be seriously aggravated, so that a clinical classification is made easily and the therapeutic approach to the problem is well defined. It has long been observed that if the patient can be brought safely through her period of menopause, be it 5 or 15 years, the hypertension will subsequently burn itself out.

Case 3.—Mrs. M. W., a 50-year-old white female, was first seen in March, 1947. She complained of severe hot flashes and nervousness for two years with increasing frequency. Just prior to this time, she had some exertional dyspnea, orthopnea, and occipital headaches associated with a blood pressure 210/110. A survey of her status at this time demonstrated no cardiac enlargement, normal urine and normal hemogram.

She was placed on estrogenic substances by mouth with the result there was a marked symptomatic improvement. She was studied further and was found to have normal renal function and metabolism rate. The electrocardiogram was normal.

Thiocyanate therapy was started, and one month later when a therapeutic blood level had been reached, the arterial tension was 190/96. These levels were maintained in the next three months; the usual level of arterial tension was around 154/86 and she was asymptomatic.

To ascertain the effect of thiocyanate better, this medication was stopped but the estrogenic substances continued. In the succeeding two months, the blood pressure rose to levels of 190/100. Roentgenogram of her urinary system at this time was entirely normal and no abnormality of the serum proteins was manifest. Thiocyanates were again started with a good therapeutic effect.

GROUP IV—The *high diastolic* type of essential hypertension as seen in the *male*, most often between the ages of 35 and 50, represents the most severe type of essential hypertension with which we have had to deal. This is indicative of either a pre-malignant phase of hypertension, or a rapidly progressive type of essential hypertension with the occurrence of heart failure, or a cerebral vascular accident, within a five year period. Unlike the female in this same age group with a severe high diastolic pressure, the male does not tolerate an increased blood pressure for a very long period of time. These patients do not respond well to thiocyanate therapy except for relatively short periods of time, and if they do show some blood pressure lability and some response to thiocyanate therapy, though it is temporary, we have subjected them to sympathectomy before the onset of renal and cardiac failure, or malignant hypertension.

Case 4.—Mr. B. K., at the age of 47, was admitted to the hospital in November, 1946. His family was free from hypertensive disease. Nocturia 3 to 4 times was pres-

ent almost an entire lifetime. In January, 1946, hypertension was found and was associated with frontal and coronal headaches of moderate severity. In May, 1946, the evening hours were marked by asthma. In the following month ankle edema was present, and in October, 1946, exertional dyspnea and orthopnea were of moderate severity.

The average blood pressure was 200/130 and was associated with the classical signs of heart failure. The retinal findings were classified as Gifford III. The hemogram demonstrated moderate hemodilution. There was moderately reduced renal function as demonstrated by the commonly employed tests and "heart-failure" urine. The electrocardiogram demonstrated a left ventricular strain pattern. Culture of the urine was negative. A standard roentgenray of the chest showed an aortic configuration of the heart with 20% enlargement. The patient's heart failure was treated in a routine manner with a reduction of the signs and symptoms of congestion. Commonly employed vasolability tests demonstrated that the blood pressure was labile; the sleeping blood pressure 155/90.

The patient was discharged from the hospital but the symptoms continued so he again was admitted for the consideration of surgical treatment. Inasmuch as all previous therapeutic attempts, including thiocyanates, had been futile, sympathectomy was advised and carried out in January 1947. A moderate amount of arteriolonephrosclerosis and slight tubular atrophy were apparent in a biopsy specimen. One month following surgery the blood pressure returned to the preoperative levels. In the third postoperative month, standing produced a diastolic rise in pressure and at the end of five minutes it was 210/140. During this time it was necessary to continue therapy for congestive heart failure and despite this in the 5th postoperative month frank decompensation was again noted. Thiocyanates were again administered and after three months the patient was able to resume 8 hours of reduced work. At this time the blood pressure ranged around 215/115. The roentgen ray showed 25% cardiac enlargement. However, the renal function tests were somewhat improved. Thiocyanates were continued at levels of 10 mg. %. In April, 1948, 14 months after surgery, frank congestion again became notable. The blood pressure ranged about 210/132 and with the aid of mercurial diuretics the patient was able to continue light work, though obviously handicapped. He was, nevertheless, in remarkably good health, considering the gravity of his initial disease.

GROUP IV B—The *high diastolic* type of hypertension in the *female*, most often observed between the ages of 25 and 40, and exclusive of those cases of hypertension which are complications of pregnancy, also represent a severe type of hypertension. However, the female hypertensive in this group, unlike the male, is much better able to withstand this severe degree of hypertension and the disease apparently progresses much more slowly. They are likely to have severe symptoms associated with the disease, which may be alleviated temporarily by the use of thiocyanates.

These patients are also of the type that are recommended for surgical sympathectomy in order to prevent, if possible, the onset of left ventricular failure.

Case 5.—Mrs. D. G. a 41-year-old white woman of Spanish extraction, was first seen about thirteen years ago. At this time, she stated that her hypertension had been found five years previously, at the age of 24. When she was 26, she had some ankle edema, and two years subsequently symptoms of headache, weakness, dyspnea, nocturnal dyspnea, palpitation and insomnia were associated with blood pressures around 220/130 mm. of Hg.



In 1935, she was admitted to the hospital because of the advent of early left heart failure. Left ventricular hypertrophy and a moderate secondary anemia were found at this time. The symptoms became so severe and unalterable under medical therapy that the splanchnic nerves and 10th, 11th and 12th thoracic sympathetic ganglia and the intervening trunks were removed bilaterally in 1935. Since this time, she has been on thiocyanate treatment and has consistently run much lower blood pressures, ranging between 175 and 200 mm. of Hg. systolic (230 occasionally) and 100 and 115 mm. of Hg. diastolic (130 rarely). She has had occasional mild signs and symptoms of heart failure associated with moderate nervous tension responding well to the usual forms of therapy. She now has considerable aortic sclerosis with no appreciable change in heart size; it still is approximately 15% enlarged. Likewise, all other signs and symptoms have not changed appreciably in these 13 years, and she is able to carry on full time duties in the business world and at home. She repeatedly states that she feels very much better and would be unable to carry on without thiocyanate treatment.

GROUP V—The *arteriosclerotic hypertensive*, usually seen in its early phases between the ages of 50 and 60, is characterized by relatively high systolic and relatively low diastolic blood pressure readings. Its course well represents the prolonged benign nature of some cases of hypertension, and although it is often accompanied by cerebral symptoms of headache, vertigo, tinnitus, and even symptoms of left ventricular failure, the disease itself is not severe and is compatible with a relatively long and useful life.

Some cases respond very well to small doses of thiocyanate but should be observed very carefully in order to avoid rapid drops in blood pressure. Other cases do not respond to thiocyanate treatment, nevertheless, the benign course of the disease is well illustrated by the following case history. Here again, however, a benign course is more likely in the female than in the male.

Case 6.—Mrs. R. T., a 75-year-old colored woman, formerly obese, was first seen 20 years ago with a moderate systolic elevation of arterial tension (BP 162/80). She complained of many bizarre symptoms which included palpitation, weakness, occasional dizziness, shortness of breath, and occipital headache. The general trend of arterial tension was upward with a greater rise of the systolic pressure. Three years later the average tension was 170/100mm. of Hg. and in another five years, the average tension was about 186/100, although occasional readings of 225/110 were recorded. Renal function tests were always normal.

About this time, diabetes was discovered and she was placed on a rigid diet which was also designed to bring about weight reduction. Still two years later her tension was about 200/93. She was given a trial on thiocyanate therapy. When adequate blood levels were maintained, her arterial tension was consistently about 165/86. She failed to follow therapeutic directions so this medication was discontinued.

From that time until the present (10 years), the patient has had to a greater or lesser degree both right and left heart failure associated with levels of arterial tension similar to those prior to the thiocyanate therapy. The usual therapeutic agents have been employed and include aminophyllin, phenobarbital and salyrgan, (92 injections). In 1947, however, occasional systolic readings of 240 were observed. Blood chemistries remain essentially normal, the roentgenray of the heart shows 15% enlargement and marked sclerosis and tortuosity of the aorta.

GROUP VI—*Malignant hypertension* is characterized by severe hyper-

tensive symptoms, including convulsions and coma. It may occur in any age group and its clinical course is rapidly progressive to a fatality. It manifests itself by a severe, progressive, generalized necrotizing arteriolar disease and renal failure. The disease shows no response to thiocyanate or any

COMPARISON of HYPOTENSIVE MEASURES

Patient -W.W. age 42

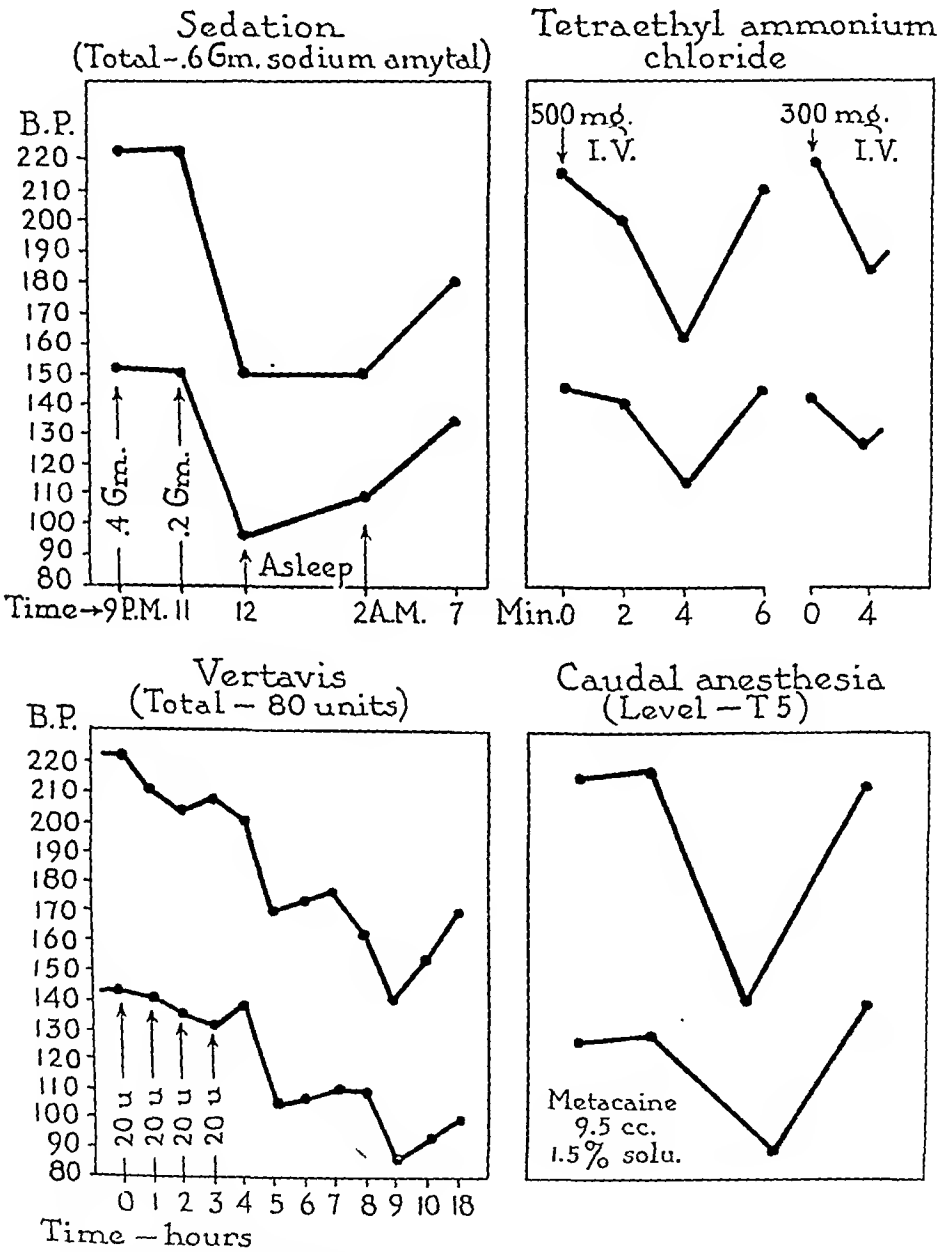


FIG. 2.—A comparison of hypotensive tests used preoperatively in patient W. W., who had high diastolic type of hypertension.

other medicinal type of therapy. A patient with any one of the types of hypertension described above may suddenly enter the malignant phase of essential hypertension and this occurrence is unpredictable and most likely to happen in the high diastolic group. Of course, a patient may be observed for the first time with the malignant type of hypertension and evidence may be un-

available that previously the symptoms of any other type of hypertension were present.

Recent reports (2, 3) seem to indicate that the rapid progress of the disease may be slowed temporarily and the life of patients with malignant hypertension may be prolonged somewhat by sympathectomy. However, there is a high operative risk in these patients and it has been our experience that immediate postoperative vascular accidents are the most common cause of death.

#### CHOICE OF CASES FOR SURGICAL TREATMENT

We chose cases from the group of patients whom we classified as belonging to *high diastolic type* of hypertension. We further restricted our

#### HYPOTENSIVE TESTS IN SYMPATHECTOMY

— Standing B.P. ---- Tetraethyl ammonium chloride

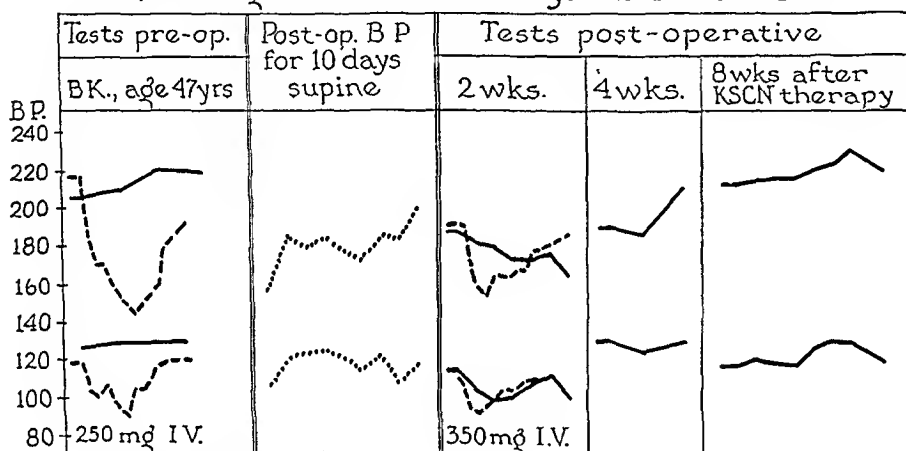


FIG. 3.—A graph showing comparison between standing blood pressures and the effect of tetraethyl ammonium chloride pre- and post-operatively on patient B. K., who had high diastolic type of pressure.

choice to those in this group who had been given an adequate and thorough trial of therapy with the thiocyanates and had proven to be resistant to this drug. That is to say, their diastolic and systolic pressures and their symptoms could not be improved by cyanate blood levels below those which produced toxic symptoms.

A third indication for the choice of patients was that they should have a labile blood pressure as evidenced by a group of pressor and depressor tests. General considerations upon which we based our surgical indications were that the patients should have systolic blood pressures over 200 and diastolic pressures over 100 mms. of mercury; that there be no evidence of chronic glomerulonephritis or pyelonephritis; no significant peripheral vascular sclerosis and that the clinical course be shown to be progressive, but not entering the malignant phase of hypertension. The average age of the patients operated upon was 40.08 years with a mean age of 39 years.

*Pressor and Depressor Tests.* We have used sodium amytal, sodium pentothal, caudal anesthesia, induced hyperpnea, tetraethyl ammonium bromide and vertavis as vasorelaxor tests, and the cold pressor tests and the administration of carbon dioxide as vasopressor indicators.

We have noted repeatedly that the most significant fall in blood pressure with caudal anesthesia occurs only when the level of anesthesia reaches the thoracic fifth dermatome. The specificity of this level in our experience is very significant and definite.

All of the patients in the high diastolic group upon whom we operated showed satisfactory responses to all the vasorelaxor and vasopressor tests used, but none of the tests gave any information whatever of the character

HYPOTENSIVE TESTS IN SYMPATHECTOMY

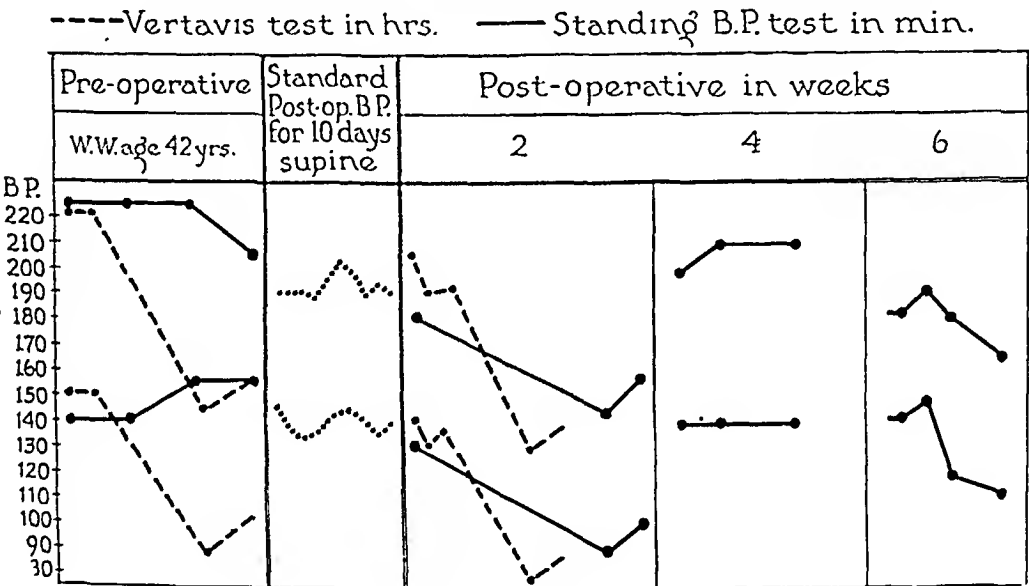


FIG. 4.—A comparison of standing blood pressure and the Vertavis test pre- and post-operatively on patient W. W., who had high diastolic type of hypertension.

or extent of the response we might expect after sympathectomy. In only two of the patients operated upon have we observed significant changes in the blood pressure readings with change of posture following sympathectomy, although in other patients the extent of the operation was identical. Figure 2 shows a comparison of hypotensive tests used preoperatively in patient W. W. From these tests alone, one could only conclude that this patient would have a satisfactory response following sympathectomy. As a matter of fact, the patient was operated upon in February; was discharged from the hospital, and in April of the same year, showed signs of a left ventricular insufficiency, complained of nocturnal dyspnea and developed a pulsus alternans. These symptoms finally culminated in a congestive heart failure which terminated fatally in October, eight months after operation. Figure 3 shows the comparison between the standing blood pressures before operation and two weeks, four weeks, and eight weeks after operation in patient

B. K. who had high diastolic type of hypertension. It also shows the blood pressure taken in the supine position ten days postoperatively. A comparison between the intravenous injection of 250 mgs. of tetraethyl ammonium chloride preoperatively and two weeks postoperatively can be compared with the intravenous injection of 350 mgs. of the same drug two weeks postoperatively. Figure 4 shows a comparison between the standing blood pressure pre-and postoperatively and the administration of Vertavis preoperatively and two weeks postoperatively on patient W. W. who had high diastolic type of hypertension. This patient's postoperative blood pressure in the supine position is also illustrated.

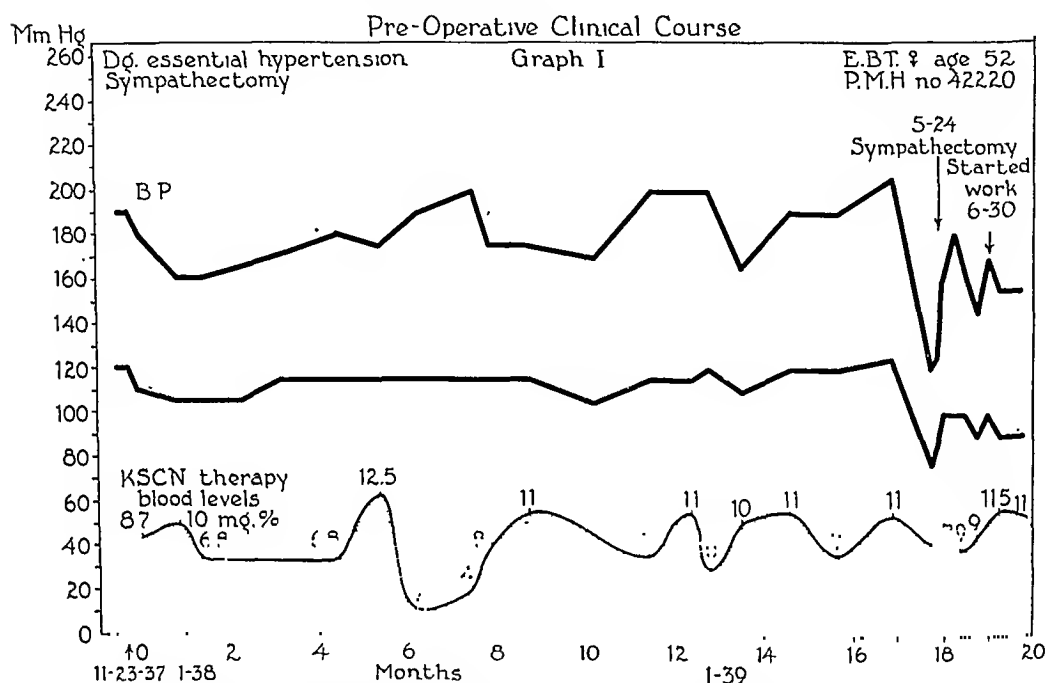


FIG. 5.—Graph 1—pre-operative clinical course on patient E. B. T. (high diastolic hypertension).

### *Surgical Procedures and Results*

This report concerns 25 patients with the high diastolic type of hypertension, who have been followed pre- and postoperatively for a sufficiently long period of time to allow us to arrive at definite opinions about them. Thirteen of these patients had supradiaphragmatic removal of the thoracic sympathetic ganglia and chains from thoracic ninth to twelfth inclusive, and the splanchnic nerves, bilaterally. Two patients had supra- and infradiaphragmatic removal of the thoracic sympathetic ganglia and chains from the ninth to the twelfth inclusive; the lumbar sympathetic ganglia and chains from lumbar one to lumbar two inclusive, and the splanchnic nerves, bilaterally. Nine patients had supra- and infradiaphragmatic removal of the thoracic ganglia and chains from the sixth to the twelfth inclusive; lumbar one, two and three ganglia and intervening chains and the splanchnics,

bilaterally. One patient had an infradiaphragmatic removal of lumbar one, two and three ganglia and the intervening chain, bilaterally.

None of the patients in this group showed satisfactory lowering of the systolic and diastolic blood pressures, or improvements in their symptoms following operation alone, which would allow them to resume their former social and economic positions. The most significant result, however, has been that whereas all of the patients have been resistant to cyanate therapy prior to operation, following sympathectomy they have become cyanate sensitive to the extent that their symptoms and blood pressure levels have been improved by the maintenance of cyanate blood levels well below those which produce toxic symptoms.

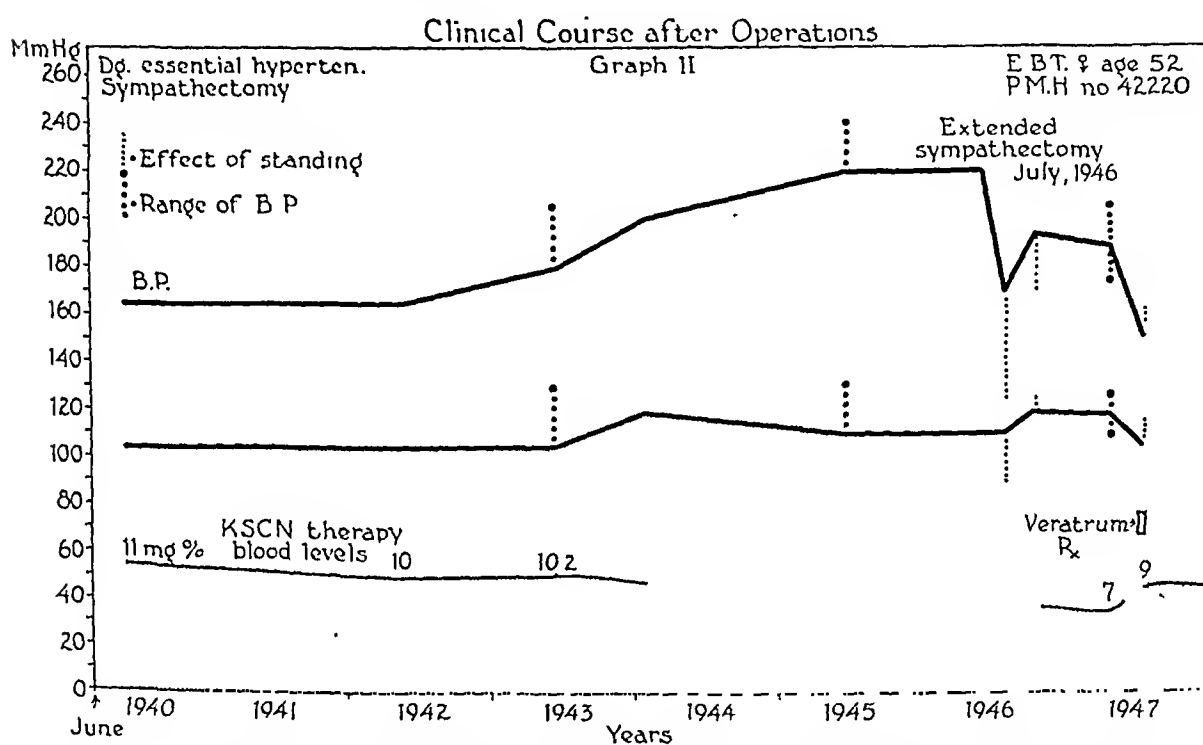


FIG. 5.—Graph 2—clinical course of patient E. B. T. (high diastolic hypertension) after first sympathectomy and extended sympathectomy.

Twelve patients in this group have died since operation so that the progression of their disease was not halted by either surgical or medical therapy. Eight of these twelve patients died within two years following sympathectomy. Four of the 12 deaths occurred immediately, during hospitalization for surgery, from heart failure and intraventricular hemorrhage.

Of the remaining 13 patients operated upon, four had their sympathectomies less than two years ago. Seven are actively engaged in their former social and economic positions and are upon cyanate therapy with excellent results. One of these patients was operated upon 13 years ago, and is actively engaged in her household and other activities with a blood cyanate level which averages about 6 mgms. percent. Before operation, her symptoms and blood pressure levels could not be controlled even with high cyanate blood levels which invariably produced marked toxic symptoms of the drug.

One other patient of this group of 13 has recurrent episodes of encephalopathy with unconsciousness; another has recently left the hospital after recovering from severe left and less severe right ventricular heart failure symptoms, and four are not actively returned to their former occupations, but are symptomatically improved. There is no doubt that the postoperative results in the high diastolic group of patients have been far better among women than men, which only re-emphasizes our original statement that

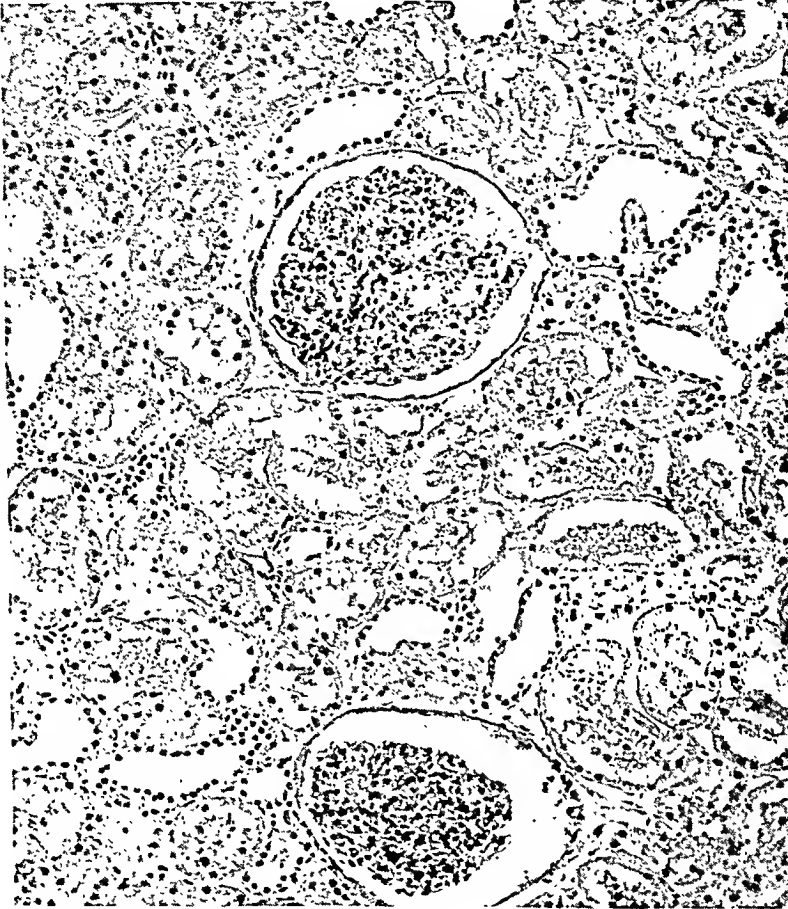


FIG. 6.—Male patient with severe hypertension, high diastolic type, with very few sclerotic changes in the terminal arterioles.

women withstand this type of hypertension better than men, but for what reason we do not know.

The following summary of the circumstances in the case of Mr. E. B. T., who was 52 years of age at the time of his operation, illustrates the results of sympathectomy in this type of hypertension:

Case 7.—Mr. E. B. T., aged 52 years, first came under observation in November, 1937, when his blood pressure was 190/120 mm. Hg. and he complained of the usual symptoms of headache, irritability, dyspnea and fatigue. He was placed on potassium thiocyanate and was so treated until May of 1939. During that time, his cyanate blood levels could be raised to 12.5 mg. % before toxic symptoms of the drug developed.

However, his diastolic blood pressure never fell below 100 mms. Hg., and his systolic pressure ranged from 160 to 200 mms. Hg.

In May of 1939, the thoracic ganglia and chain were removed bilaterally from thoracic ninth to twelfth inclusive, and the splanchnic nerves were resected.

The patient returned to his work in June of 1939 and was maintained on cyanates and with blood pressures averaging 160 systolic and 100 diastolic. In 1943, his blood pressure readings began to rise following cessation of thiocyanate therapy and in 1946 the systolic pressure reached 220 and the diastolic remained at 100. He was operated upon again in July of 1946 at another hospital where the lumbar ganglia and chains were removed and the thoracic chains removed with the ganglia up to thoracic

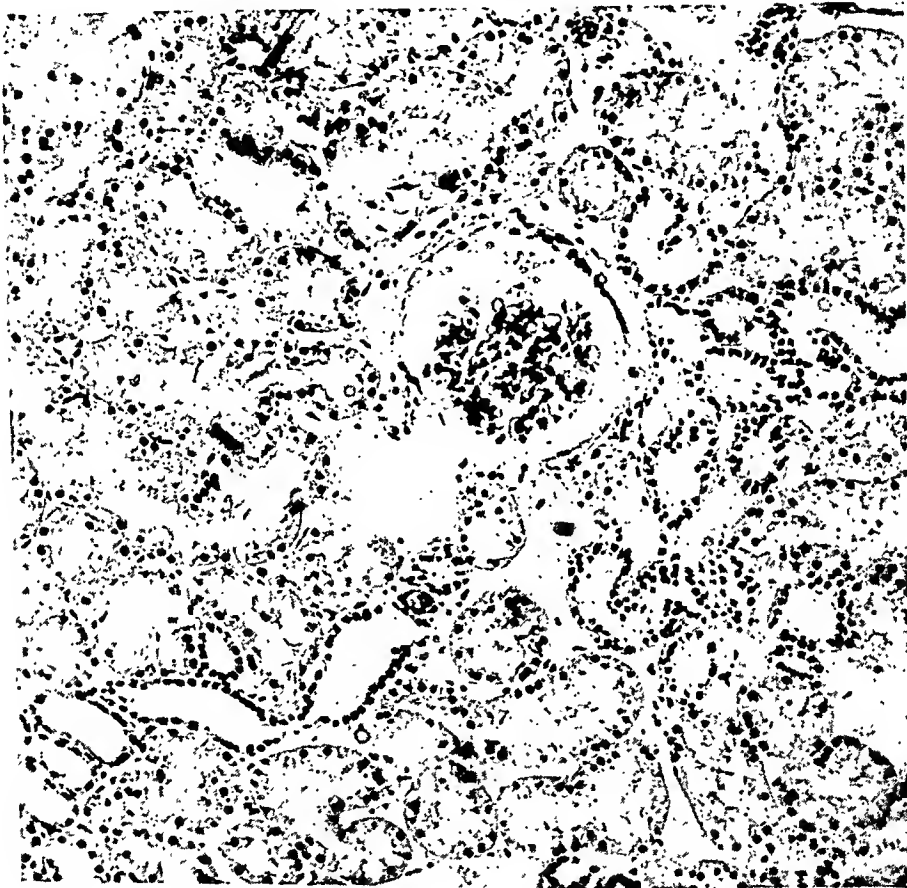


FIG. 7.—Female patient with moderate hypertension of the high diastolic type, with extensive sclerosis in the arterioles.

fifth bilaterally. Following this operation, this patient showed a definite postural hypotension. He was placed upon veratrum therapy and shows lower blood pressure levels, particularly the systolic reading which has been recorded as low as 140 mms. This may possibly be the first indication of impending congestive heart failure. However, he now shows a reversal of his blood pressure levels upon standing and both the systolic and diastolic readings are higher upon standing than when lying. (Fig. 5)

We have previously reported that we have been able experimentally in dogs and monkeys to produce hypertension by the Goldblatt clamp and by wrapping the kidneys in silk, which responds to the administration of the thiocyanates exactly as do hypertensive symptoms in man. We have been unable as yet to explain the site or nature of the effect of the thiocyanates,



nor why this group of patients resistant to the drug before operation, become sensitive to the cyanates following sympathectomy.

#### BIOPSY SPECIMENS OF KIDNEYS

We have taken specimens of the kidneys at the time of operation and have examined the kidneys microscopically after autopsy in an effort to correlate the clinical symptoms and course with the pathological changes in

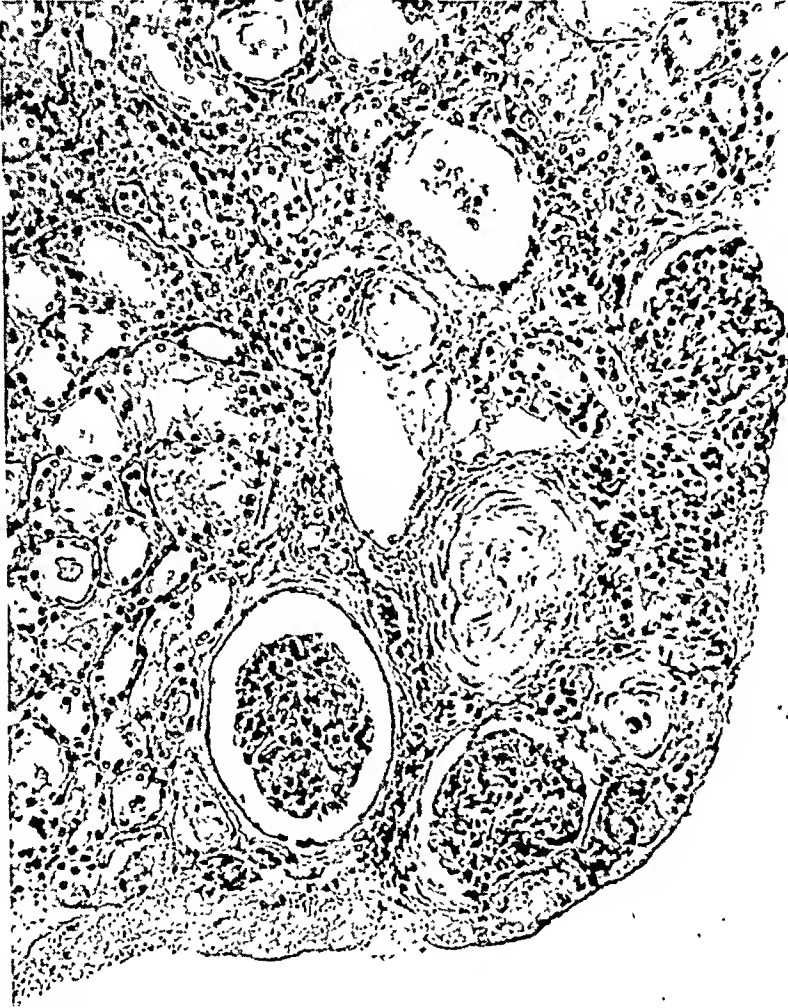


FIG. 8.—Male patient with hypertension of the high diastolic type with low grade sclerotic changes in the arterioles and sclerosis in the arteries.

the kidneys in an effort to draw the indications for surgical therapy more accurately.

Figure 6 is a microphotograph of a specimen of the kidney of a patient who clinically had a very severe hypertension of the high diastolic type. One must look very carefully to find any sclerotic changes in the terminal arterioles. Figure 7 is a microphotograph of a specimen of the kidney of

a patient who had the symptoms of what was judged to be clinically a moderate hypertension. Yet, the sections of her kidney show a rather extensive sclerosis in the arterioles. This patient is one of the best of the postoperative results following sympathectomy.

We have been unable to find any correlation of the pathological changes in the kidney and the function in these cases of hypertension which would be useful in choosing those patients unsuitable for surgical treatment. Arterial sclerosis in the kidney may come with age alone. It is the combination of arteriolar and arterial sclerosis which is pertinent in the cases of hypertension. Evidence of arteriolar sclerosis may be very hard to find in the specimens removed for study, or it maybe quite evident, irrespective of the severity or mildness of the clinical symptoms and course. Arterial sclerosis without arteriolar sclerosis may be present in hypertension but not arteriolar without arterial sclerosis. Figure 8 is a microphotograph of a kidney specimen from a patient with a clinical high grade hypertension of the high diastolic type. The changes in the arterioles are present but low grade in extent and the arteries show sclerosis.

#### SUMMARY

1. Sympathectomy alone has not been successful in permanently reducing the blood pressure levels in the high diastolic type of hypertension regardless of the extent of the operation. However, in some cases the subjective symptoms have been improved temporarily although the clinical course of the disease has remained unchanged.

2. Sympathectomy has caused patients in this group who have been resistant to thiocyanate therapy preoperatively to become sensitive to the administration of this drug. This result has been confirmed by laboratory experiments upon monkeys and dogs. The physiological explanation for this effect has not as yet been explained to our satisfaction.

3. There has been no significant change in the blood pressure levels, or heart size, unless the patients of this group have been given thiocyanates postoperatively.

4. In the high diastolic type of hypertension vasopressor or vasorelaxor tests have not proven to be sufficiently accurate to say exactly which of these patients should be operated upon.

5. The medical management of patients of this group, particularly with the administration of thiocyanates properly controlled, is good in the early stages of the disease, but sooner or later all have become resistant to this drug.

6. We believe that the results of surgical therapy in patients with hypertension can be evaluated only by a comparison with specific groups of patients belonging to types of hypertension based upon their clinical symptoms and course. Those types of hypertension which have been shown to respond well to medical management, we believe, will show good results

from surgical therapy alone, but the selection of patients for operation should be made, not upon blood pressure ranges alone, but upon the characteristic symptoms and clinical course of the disease. Until comparison of the results of surgical therapy is made upon accepted classifications of the clinical symptoms and course of this disease, confusion in interpretation of the surgical results will exist.

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# GANGLIOSYMPATHECTOMY AND BILATERAL HEMIADRENALECTOMY FOR SEVEREST GRADE OF HYPERTENSION\*

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BECAUSE RESULTS ARE OFTEN UNPREDICTABLE, uncertain, and transitory, sympathectomy is not generally advocated for the severest grades of hypertension. I began to add various procedures to the customary dorsolumbar operation about seven years ago in the hope of improving the result in such cases. They consisted of denervation of the adrenal glands, stripping of the adventitia of the lower thoracic aorta, and subtotal removal of the semilunar ganglia. Finally all were employed without any consistent improvement in results.

The addition of procedures on the adrenals was then undertaken. One adrenal was removed in each of a few cases, apparently without effect. The next procedure, was employed in only one case, excision of half of one adrenal and complete removal of the opposite one at the second stage sympathectomy. The procedure proved to be too drastic possibly because of contralateral hemorrhage which has been noted to occur experimentally. A profound drop in blood pressure was combatted for several weeks by heroic measures. An adrenal transplant was without definitive effect and the frequent administration of cortex has been required in order to maintain a systolic pressure between 110 and 120. An Addisonian symptom-complex, including pigmentation, has developed. The case is possibly unique insofar as the cure of hypertension is concerned but at the expense of what appears to be permanent adrenal insufficiency.

Subsequent operations, now 14 in number, consisted of the removal of approximately the upper half of each adrenal gland at the time of sympathectomy. The operative procedure can be outlined briefly. Under intratracheal anesthesia the entire twelfth rib and usually a substantial paravertebral section of the eleventh are removed. The thoracic dissection is extrapleural. The sympathetic trunk is divided at the level of the fourth or fifth ribs and is freed to the diaphragm. The splanchnic is similarly treated, the thoracic aorta being exposed in this step. The adventitia of the lower thoracic aorta, which bears sympathetic fibers, is freed and excised down to the diaphragm. The latter is severed locally to the region of exit of the sympathetic nerves into the retroperitoneal space, in order to simplify their further dissection and to aid in some measure in the exposure of the adrenal. The greater splanchnic is dissected to the semilunar ganglion which is excised almost to the aorta. The sympathetic trunk is freed to the second lumbar ganglion below which it is removed. The adrenal gland, previously inspected to ascertain if it were the seat of a neoplasm, now is brought into

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\* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

full view by suitable retractors and the removal of overlying fat (when present). The upper half is dissected free with meticulous attention to hemostasis. In order to remove the upper half without hemorrhage chain sutures are passed and tied gently and the adrenal detached step by step beyond the line of sutures. The result usually has been the removal of somewhat more than half the adrenal. However the main blood supply which enters the lower half remains intact. Virtually the same operative procedure on both adrenals, in addition to bilateral sympathectomy, semilunar ganglionectomy and stripping of the adventitia of the aorta, was performed in each of the 14 patients.

A brief reference should be made to the types of operative cases before mention is made of the results of operation. The preponderance of the patients suffered from the severest forms of hypertension with systolic ranges from 250 to 300, diastolic from 150 to 190. A number were in the older age group. The first operation having been performed less than three years ago, reference can be made to interval results alone. There has been no mortality and but little morbidity. The low morbidity is ascribable to the fact that the pleura is rarely entered and if entered sutured, and the trapped air withdrawn at the end of operation.

There was one failure to influence the blood pressure. This was the only case in which microscopic examination of the removed adrenal revealed generalized arteriosclerosis. In addition to the usual symptomatic relief, the result of operation in 13 cases has been a pronounced reduction in blood pressure, below the 200 systolic level in most instances, with proportionate reduction in the diastolic level. Lability of blood pressure has been evident in more than half the cases. However, the striking feature has been a persistent, pronounced, but nevertheless symptom-free postural hypotension. A drop from 180 to 130 noted a year or more after operation has not been unusual.

Bilateral hemiadrenalectomy was employed in three cases of severe hypertension after sympathectomy had failed, with pronounced improvement in two and little improvement in one. Hemiadrenalectomy, performed on one side in three cases, was not attempted on the other because too great a reduction in blood pressure was feared at the time of completion of the sympathectomy on the second side. The results were satisfactory in these three cases but they did not belong to the severest grades of hypertension. However, the uncertain results obtained in severe hypertension raise the question of the addition of unilateral or even bilateral hemiadrenalectomy in cases short of the most severe forms of hypertension. Finally, the influence of bilateral hemiadrenalectomy on blood pressure appears to be so salutary as well as distinctive that the question of employing this procedure alone for hypertension naturally arises. Theoretically at any rate, subtotal adrenalectomy for hypertension appears to parallel subtotal thyroidectomy for Graves's Disease.

## SYMPATHECTOMY IN HYPERTENSION

DISCUSSION.—DR. A. W. ADSON, Rochester, Minn.: I have enjoyed these papers and commend Dr. Davis for his conservative attitude in employing extensive splanchnic nerve resections in the treatment of hypertension. Our experience corroborates Dr. Davis' report in that the administration of cyanates often is more effective in lowering blood pressures following splanchnic resections than they were when administered prior to surgery.

The reports of Crile and DeCorsey prompted me to resect one-half of each adrenal gland at the time of operation when I resected the splanchnic nerves, a portion of the celiac ganglion and the upper two lumbar sympathetic ganglia in 25 consecutive cases. The postoperative results in those patients appeared to be no different than those obtained from the extensive sympathectomies. Our observations probably were very similar to those reported by Dr. Neuhof.

As many of you know, we at the Mayo Clinic have been interested in controlling essential hypertension by operative procedures on the sympathetic nervous system. In 1930, while observing the blood pressures fall in a patient who had been given a spinal anesthetic for a pelvic operation, it occurred to me that a bilateral rhizotomy of the anterior roots of the spinal nerves from the sixth dorsal to the second lumbar inclusive should produce similar falls in blood pressures to those that resulted from the spinal anesthetic, since the white sympathetic rami carrying vasoconstrictor impulses would be interrupted and paralyzed just as they were during the spinal anesthetic. The operation, a laminectomy and rhizotomy, was employed in 30 cases. It was discontinued because of its magnitude and the surgical shock that resulted from the marked hypotension. The subdiaphragmatic approach was substituted for the laminectomy and rhizotomy.

The subdiaphragmatic approach through the loin was extraperitoneal. The kidney and liver were retracted mesially with a broad illuminated retractor which readily exposed the splanchnic nerves, the celiac ganglion and the upper portion of the sympathetic lumbar chain including the first and second lumbar ganglia. The splanchnic trunks were resected as was a portion of the celiac ganglion and the upper lumbar chain. The immediate effect was a marked hypotension. The late results showed that about one-third of the patients remained well. They were free from symptoms and blood pressures remained within normal levels. One-third of the patients developed a gradual rise of blood pressures within two to four years but still were free of symptoms. The last one-third of the postoperative group responded less favorably. Blood pressures and symptoms returned to preoperative levels within six to 12 months.

In view of the fact that other operations such as resection of the splanchnic trunks by the supradiaphragmatic approach and by the thoracolumbar approach which includes a portion of the celiac ganglion and the upper lumbar chain, we, the neurosurgeons at the Mayo Clinic are employing the different operative procedures in order to compare the effectiveness of each. At present, it appears that the late results following surgery are very similar regardless of the technic employed.

Since Dr. Crile in treating hypertension may not have completely removed the celiac ganglion by the tactile and avulsion method, and in the light of the investigative work on vasospasm of renal arteries in shock by Trueta and collaborators, I have resected the celiac ganglion under direct vision, making sure to include the aortico-renal ganglion, for essential hypertension. The object of this radical resection is to also interrupt the postganglionic sympathetic fibers to the adrenal glands and kidneys. The immediate postoperative hypotension is as marked as it was following the extensive rhizotomy. The postoperative shock is much less than the shock and sequela following thoracolumbar procedure.

I still am not too thoroughly convinced that regeneration of sympathetic fibers takes place, and this is especially so if a gap of three centimeters is left between the severed ends. As a matter of routine, I usually apply a silver clip on the sectioned

ends of the sympathetic nerves or trunks to control any bleeding that might take place. However, the silver clip may have taken on a more significant role since a silver sulfide develops in the vicinity of the clip, which destroys and fixes neurogenic tissue. The lantern slide of such a specimen illustrates the point. The two specimens on the slide are from a patient upon whom I had operated ten years previously for hypertension, by the subdiaphragmatic method. At that time, I applied a silver clip on the proximal ends of the splanchnic trunks. Since this patient's blood pressures gradually rose to preoperative levels, Dr. Craig advised that another operation be done, and he removed the thoracic portion of the splanchnic trunks. As you observe, the lower end of the specimen is black in appearance, a portion of silver clip still remains, the neuroma consists chiefly of fibrous tissue, and there is no evidence of regeneration.

I still believe that our greatest problem in attempting to manage the treatment of essential hypertension is to select the patient for the particular type of treatment, whether it be medical or surgical treatment. If it is to be surgical treatment, employ it before irreversible changes have taken place in the cardio-renal-vascular mechanism.

# MANAGEMENT OF MASSIVELY BLEEDING PEPTIC ULCER\*

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OPINION CONTINUES TO BE DIVIDED on the management of gross bleeding from peptic ulcer, even though clinical experience is distressingly ample in most large teaching hospitals. Reasons for confusion of thought evident in the literature of the subject are lack of precise clinical observations and careful reporting, lack of definite criteria in the selection of cases to be treated in any particular manner, variation in the quality of medical or surgical care provided, and what may be called clinical bias. Various authors have focused attention on the life-saving value of early surgical control of hemorrhage in these cases, but the ideas developed in their pioneer work have not as yet won the enthusiastic support of gastroenterologists 1-9.

It has seemed to us that advances in surgical technic and care, improvements in anesthesia, and sounder knowledge of hemorrhagic shock and its treatment<sup>10 11</sup> warrant further careful evaluation of the merits of rapid blood replacement and early surgical operation in this condition. Accordingly, since January 1947 we have been testing the value of immediate large blood transfusions and gastric resection in the therapy of grossly bleeding peptic ulcer, and though the work is still in progress it is justifiable to report on methods used, clinical results to date, and tentative conclusions. At present the series comprises 54 patients, 33 of whom were operated upon, and 21 of whom were treated as control cases without operation.

A definition of terms and explanation of criteria used in the selection of cases is in order. By early operation we mean subtotal gastric resection within 24 hours of admission to the hospital. By acute hemorrhage is meant vomiting of blood or passage of blood by rectum with attendant signs of cerebral anoxia within one week of admission to the hospital. To be classified as massive the hemorrhage must have been severe enough to depress the admission red cell count to 2.5 million per cmm or less, or to reduce the circulating red cell volume to 60 per cent of normal or less. Our criteria in the selection of cases in which early operation is recommended may be tabulated, therefore, as follows:

1. The patient must have bled grossly into the upper gastro-intestinal tract within one week.
2. The admission red cell count must be 2.5 mill/cmm or less, or the circulating red cell volume must be 60 per cent of normal or less.
3. There must be reasonably good evidence for the diagnosis of peptic ulcer.

In addition, at least three liters of properly matched blood must be immedi-

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ately available. Operation is advised and carried out at once when these circumstances are present. If the bleeding has been less severe, or conditions are otherwise than as outlined, a non-surgical regimen is instituted and tests are repeated 24 hours later, or with the appearance of further signs of hemorrhage. If the patient or his referring physician show reluctance toward recommended operation, the patient is put into the control series and is treated otherwise as nearly similarly as possible. Blood is given freely and food is allowed as tolerated. Grave associated disease has not constituted a contraindication to operation in this series of cases, but rather the contrary. It seems reasonable that the rapid relief of anoxia and surgical control of hemorrhage would increase rather than impair the patient's ability to survive previously existing disease. Consequently, we have operated upon patients with advanced bilateral tuberculosis, hypertensive cardiovascular disease, extreme obesity, coronary sclerosis, pulmonary emphysema, chronic sepsis and cerebral hemorrhage. If the patient shows signs of hemorrhagic shock, the rate of administration of blood and preparation for operating are speeded up. In several instances operation was started within two hours of admission, while the patient was still hypotensive, but blood was being transfused rapidly at the same time.

Within one-half hour after admission to the hospital blood studies are made by a trained laboratory team, and blood transfusion is started immediately after samples are taken. The measurements include red cell count, hemoglobin and hematocrit, plasma volume, extracellular fluid volume, plasma protein concentration and non-protein nitrogen, plasma chloride and  $\text{CO}_2$ -combining power, and blood sugar. The analytical methods used are standard methods with which the laboratory staff has had considerable experience<sup>12</sup>. The blood smear is studied for type of anemia and abnormal elements, and the clotting mechanism is investigated to exclude the presence of hemorrhagic diathesis. All blood given the patient is weighed and its hemoglobin and protein content are determined beforehand. Blood loss at operation is measured and in 29 gastric resections in this series averaged 365 cc. Urine volume is measured daily and its content of cells and albumin and its specific gravity and pH are determined. In no instance was the lower nephron syndrome encountered. In patients operated upon liver biopsy is done as soon as the peritoneal cavity is opened, and the glycogen content of the specimen is measured. The blood studies are repeated within 24 hours after the operation, and again before discharge from the hospital.

The program of treatment may be briefly outlined as follows: If the criteria described are fulfilled, operation is advised within one hour after admission to the hospital, regardless of any associated disease, unless the patient is moribund from some cause other than hemorrhage from peptic ulcer. The anesthesia has been ether-oxygen mixture by endotracheal tube at the hands of a senior staff physician anesthetist. Blood is given through two cannulas before and during operation, and to a less extent afterwards.

The average interval between admission and operation has been 9.2 hours, most of which delay is occasioned in obtaining the necessary amount and type of blood.

At operation subtotal gastric resection is done with antecolic Hoffmeister anastomosis, an average of 80 per cent of the stomach being removed as shown by actual measurements. If it is a posterior wall duodenal ulcer, where feasible the ulcer is dissected out. In some instances the procedure described by Allen is employed<sup>4</sup>. In two cases the posterior wall duodenal ulcer had so large a crater and was surrounded by so much acute inflammatory reaction that pyloric transection was deemed advisable. An interesting problem confronts the surgeon when at operation no lesion of stomach or duodenum can be detected and no cause for hemorrhage can be made out after careful abdominal exploration. In this situation extensive gastric resection is performed without hesitation. In 5 such instances the resected specimen has shown shallow ulcers with open vessels, the stomach being involved in 4 cases and the duodenum in one.

TABLE I

	R.B.C. Mill/cmm	Vc %	Circ.Vol. R.B.C. % Norm.	Plasma Protein Gm/100cc	Plasma Volume % Norm.	Serum N.P.N. Mg/100cc
Operated on .....	2.5	26	48	6.0	100	53
Not operated on .....	2.9	29	55	5.9	97	43
<i>Average Values for Admission Laboratory Data in Patients with Acute Massive Hemorrhage from Peptic Ulcer (Early Operation in 32, No Operation in 21)</i>						

An important technical point in some cases is evacuation of the stomach by gastrotomy before proceeding with gastric resection. The stomach is sometimes distended by a jelly-like cast of blood, and if the clot is carefully milked out through the transected lower stomach extensive gastric resection then becomes feasible.

Following operation penicillin and oxygen therapy are provided, and in the later cases streptomycin. The patient is out of bed within 24 hours for early ambulation. Sodium bicarbonate or sodium lactate is given intravenously to maintain alkalinity of the urine. As a rule little blood is given postoperatively. The average period of hospitalization following operation has been 15 days.

Of the 54 patients in the series to date 33 were operated upon early, and 21 were not operated upon, due to disinclination on the part of the patient or the referring physician. Four of the patients operated upon were found to have other causes for bleeding rather than gastroduodenal ulcer. One had esophageal varices, one hiatal hernia and peptic ulcer of the esophagus, one carcinoma of the cardia and one lymphosarcoma of the stomach. In the latter case gastric resection was performed, in the others only exploratory laparotomy. All four patients made uneventful convalescence.

With regard to diagnosis, reliance has been placed chiefly on the history and physical findings. The passage of stools containing fresh or tarry

blood had been noted by 44 of 50 patients, while 37 had vomited blood. All had either melena or hematemesis. The majority of the patients gave a history of ulcer dyspepsia, though in seven cases the symptoms were of less than six weeks' duration. In 16 patients a diagnosis of peptic ulcer had previously been made by roentgen studies. The most important physical findings were pallor, peripheral evidence of shock, and epigastric tenderness. Blood in the stool and in the gastric contents was also important. Of the entire group of 54 patients 24 showed signs of hemorrhagic shock on admission. Of these 24 patients 15 were in the operative group and the opera-

TABLE II

	Number	Average	Age High	Low	Average	Blood given, cc High	Low
Operated on early .....	33	54.6	74	22	3,600	9,400	1,000
Not operated on .....	21	61.0	82	35	2,040	11,000	0

*Age and Amount of Blood Given in Patients Operated Upon Early and in Patients Treated Non-Surgically for Acute Massive Hemorrhage from Peptic Ulcer*

tion was not postponed but resuscitation and operation were carried out concurrently. The roentgen ray has not been used as a diagnostic aid in this series of cases, as in our judgment the findings of examination under these difficult circumstances are not definitive enough to warrant delay and further manipulation.

Pathologically the bleeding ulcers of this series have fallen into two groups. More numerous have been the deep large indurated ulcers of stomach or duodenum, and often these lesions have penetrated neighboring structures. Less common have been the single or multiple shallow ulcers of stomach, or less often of duodenum, with little or no external or serosal evidence to suggest their presence. These lesions are usually associated with

TABLE III

	R.B.C. Mill/cmm	Blood Volume % Norm.	Total Cir. Hb. % Norm.	Plasma Protein Gm/100cc	Plasma Volume % Norm.	Total Cir. P.P. % Norm.	Serum N.P.N. Mg/100cc
Admission .....	2.5	78	40.0	6.0	100	86	53
24 hours .....	3.8	95	68.7	6.2	110	99	41
Discharge .....	4.0	95	70.8	6.6	104	100	28

*Average Values for Laboratory Data in 32 Patients Operated Upon Early for Acute Massive Hemorrhage from Peptic Ulcer*

a short history. Hemorrhage may be fatal from these rather trivial looking lesions. The single marginal ulcer in the series to date followed gastroenterostomy done many years previously, and gastric resection had to be supplemented by resection of jejunum and transverse colon and cecostomy. Convalescence was satisfactory despite the extent of the operative procedure.

In Table I are shown admission laboratory data obtained prior to treatment in 32 patients operated upon, as compared with 21 not operated upon, average values being shown. The severity of the anemia is obvious. In appraising this factor one must always consider volume as well as concentra-

tion. The reaction to severe hemorrhage consists of shrinkage of circulating blood volume as well as anemia, hence these two laboratory findings must be taken together in setting up criteria for operation and for later assessment of the patient's condition. Plasma protein and plasma volume are far less critical factors in the survival of the patient than total circulating hemoglobin, and in both groups of patients plasma volume was normal on admission. The group treated by early operation are shown to have been more depleted than the group of patients in the control series, particularly with respect to hemoglobin values. The higher non-protein nitrogen figures probably indicate greater blood loss in the group operated upon.

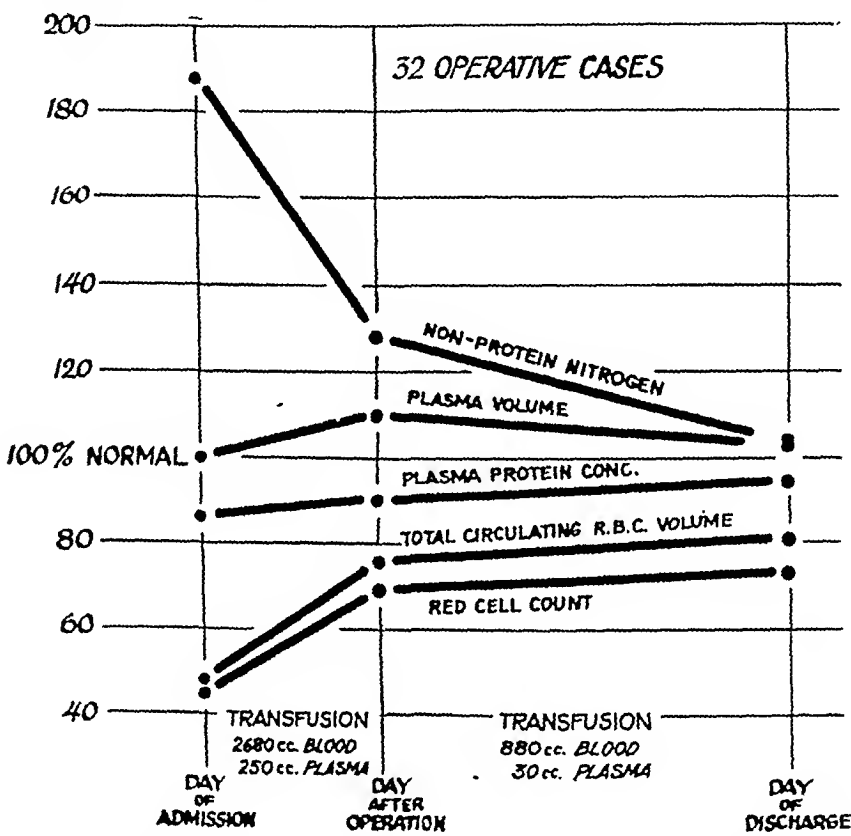


CHART I.—Study of effects of transfusion therapy on total circulating plasma protein and total circulating hemoglobin in ten cases.

In Table II appear data on age and blood transfusion therapy in the two groups of cases. Both groups of patients fell into the older age brackets, in which mortality rate is higher. It happened that the average age of the control group was somewhat greater than that of the group treated by early gastric resection. The patients operated upon received an average of 3600 cc. blood, as compared with 2040 cc. for the control group. In the control group one patient received no blood, as he died of hemorrhage within one-half hour after admission. Conditions were not strictly comparable, therefore, in the two groups of cases, though reasonably similar circumstances prevailed except for the factor of surgical operation. The patient in the non-operative group who received 11,000 cc. of blood eventually succumbed to hemorrhage.

In Table III are shown laboratory data before and after treatment in the group of patients operated upon. It is notable that total circulating hemoglobin values remained at less than 75 per cent of normal despite the administration of 3600 cc. blood, average values being considered. This raises the question of the physiologic nature of the adjustments to hemorrhage and of the subsequent reaction to replacement therapy. In Chart I are indicated further computations bearing on this subject. In 10 patients treated by early gastric resection an effort was made to determine how much of the administered hemoglobin and plasma protein remained in circulation. In all cases the hemorrhage was completely controlled by operation, and there was no reason to believe further bleeding occurred. Processing losses and losses of blood at operation were included in the computations. It is evident

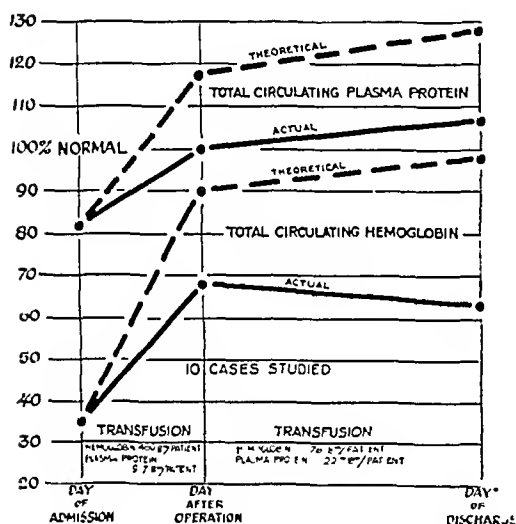


CHART II.—Average values for laboratory data in 32 operative cases of massively bleeding peptic ulcer.

that the total circulating plasma protein quickly returned to normal and remained there, despite the administration of 20 to 25 per cent in excess of that theoretically required to achieve normal values. Presumably such excess plasma protein becomes a part of the "metabolic pool," as pointed out by Whipple<sup>13</sup> and Allen, Bogardus, Egner, and Phemister<sup>14</sup>, and is subject to the demands of nitrogen metabolism. With respect to the fate of hemoglobin administered in theoretical surplus, the explanation is more difficult. At the end of 24 hours 22 per cent of the administered hemoglobin has apparently left the circulation, while at the end of 15 days 35 per cent is "missing," even though a serious anemia is present.

There was no evidence of hemolysis in these cases as a possible explanation for the discrepancy. It is conceivable that the body reservoirs of hemoglobin, called upon in life-endangering hemorrhage, demand repayment of the loan as soon as physiologic stress is relieved. Further investigation of this question is in order. Whatever the explanation for this finding, its practical significance is that much larger amounts of blood are required in the replenishment therapy of hemorrhage than is usually realized. Unquestionably these patients have been given too little blood in the past, whether operated upon or not. Incidentally, we have seen no evidence of over-transfusion in any patient studied. Despite the frequent presence of hypertensive arteriosclerotic heart

disease in these patients, in none have we seen pulmonary edema, as described by Eaton in animal experiments<sup>15</sup>, or congestive failure.

In Chart II are shown in graphic form average values for plasma protein concentration, plasma volume, red cell count and total circulating red cell volume before and after treatment in 32 patients operated upon. The average interval between points 2 and 3 was 15 days. The rapid decline of the initially elevated serum non-protein nitrogen to normal is worthy of note.

Table IV contains data bearing on carbohydrate metabolism. Elevation of blood sugar was found to be the rule in the hemorrhagic state, and the

TABLE IV

Blood Sugar Mg/100cc			Hepatic Glycogen Gm/100Gm		
Average	High	Low	Average	High	Low
164	300	112	2.9	6.2	0.3

*Blood Sugar and Hepatic Glycogen Values (Liver Biopsy) in 16 Patients Operated on Early for Acute Massive Hemorrhage from Peptic Ulcer*

TABLE V

	Number	Deaths
Patients treated surgically.....	33	5 (15%)
Gastric ulcer .....	12	3
Duodenal ulcer .....	16	2
Marginal ulcer .....	1	0
Other lesions .....	4	0
Patients not operated on.....	21	6 (29%)

*Results from Early Operative and Non-Surgical Management of Acute Hemorrhage from Peptic Ulcer*

average value of 164 mg. per 100 cc. is to be compared with the normal of 80 to 120 mg. per 100 cc. for the method used. In 16 cases just after the peritoneal cavity was opened the liver was biopsied and the glycogen content of the sample was measured. Definite reduction in hepatic glycogen was the rule. Presumably both these findings are related to activity of the sympathico-adrenal system, and possibly also to preceeding deficiency in caloric intake. The evidence indicates the need for the early administration of an adequate caloric supply to these patients.

In Table V the mortality rates in the two groups of cases are indicated. The series is hardly large enough to warrant statistical analysis, but those of us concerned with the work believe that more lives are being saved by the program of early adequate blood replacement and gastric resection than by the non-surgical plan of treatment. The surgical resident staff, on whose shoulders falls the major part of the work of this rather gruelling program, are among its most enthusiastic proponents. If the resident staff is truly convinced of the value of a method—as all chiefs of teaching clinics know—the method must have real merit.

In conclusion, evidence has been presented which tends to favor early restoration of hemoglobin values and gastric resection as the method of

choice in the management of acute massive hemorrhage from peptic ulcer. The advantages of the method as seen at present are:

1. Hemorrhage is controlled directly
2. Mortality rate is lowered
3. Definitive treatment is provided for the peptic ulcer diathesis
4. Early resuscitation and relief of anoxia is achieved
5. Diagnosis is established in doubtful cases
6. Pyloric obstruction when present is relieved
7. Less blood is required in many cases

The method is not to be recommended, however, unless adequate facilities are at hand, and these may be summarized as:

1. Expert 24-hour laboratory service
2. Adequate blood bank
3. Skillful anesthesiologic service.
4. Expert surgical judgment and technique
5. Expert resident and nursing care

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DR. ALLEN O. WHIPPLE, New York: I do not know of anything more trying or more difficult than to be called in consultation on a patient who has been bleeding for days, and finally the medical group call in the surgeon to advise further therapy. Many

of these patients are in a marked state of depletion, they are the worst kind of surgical risks, and when the surgeon advises surgery he is faced with a very difficult problem. Furthermore, many times exploration has been done in an attempt to find the bleeding point or stop the bleeding, and because of the condition of the patient attempts to resect them have not been made. That type of surgery is not very effective. It seems to me that when this type of case is seen early and there has been severe bleeding, the indication for extensive transfusion is very definite, and in that respect indications differ from those where extensive operations are done but the patients are over-transfused. I am sure that many patients at present are being over-transfused in operations where they have not lost a great deal of blood, but where transfusion has been given on the theory of prevention of shock. I am sure, as Dr. Stewart has said, that this question should be very thoroughly investigated. In fact, I heard a short time ago of a patient who had to have a phlebotomy because he had been given too much blood.

In regard to patients with the type of ulcer most conducive to severe hemorrhage, that is, the ulcer situated in the lateral mesial aspect of the duodenum, where resection of the stomach will not necessarily control the bleeding, there is one point that seems to me worth considering; that is, to identify the gastroduodenal artery and ligate it. Of course the inferior pancreatico-duodenal may continue to be a source of hemorrhage, but I think the majority of cases bleed from the superior pancreato-duodenal artery, and for that reason ligation of the main arteries entering the ulcer is an added safeguard.

This series that Dr. Stewart has reported seems to me to be very timely, and emphasizes the importance of not delaying surgery too long in the care of the severely bleeding gastric or duodenal ulcer.

DR. EDWARD D. CHURCHILL, Boston: Dr. Stuart has introduced a fundamental problem of hemorrhage. As surgeons, we have been concerned with the immediate effects of acute massive hemorrhage; in other words, the effects on the intravascular blood volume, and have focussed our effort on the development of resuscitative measures to control shock. Once the patient had recovered from the acute crisis, however, it was felt that the job was finished. If the patient had a residual hypochromic anemia, it was thought time and iron therapy were sufficient. I am quite certain that this is the point of view now held by many internists with regard to hemorrhage from ulcer. If the patient survives the immediate crisis of hemorrhage, then the residual hypochromic anemia is a simple medical problem. The real tragedy comes when a second emergency arises before complete compensation is established. This is an event peculiar to bleeding ulcer and not infrequent. I have heard it pointed out repeatedly by Dr. Allen that such a patient cannot tolerate the crises of further hemorrhage and surgical operation. This is a very sound observation, and Dr. Stewart is posing the question of why it is true.

The data presented on the disappearance of hemoglobin (54 hours after replacement therapy, 22 per cent hemoglobin missing; and after fifteen days, 35 per cent hemoglobin missing) raise important problems. Dr. Stewart suggests tentatively that the body is recalling the hemoglobin for its stores. He finds no evidence of hemolysis. It is useless to speculate, but the hypothesis should also be entertained that the body may be calling on the red cells for something other than hemoglobin. Dr. Stewart himself, a number of years ago, showed the diuresis of potassium that occurs after massive hemorrhage. In the face of generalized depletion in intracellular electrolytes, possibly the body calls for any excess balance of these items carried by the red cells.

A similar situation was encountered in the management of battle casualties. There was acute massive hemorrhage associated with the wounding, massive blood replacement—more blood than was lost, perhaps—to get the patient through the crucial initial



surgery, and yet two or three days later when the wounded man arrived at a general hospital, a profound anemia existed. These observations of Dr. Stewart link in with other studies that are being carried on. Those of Dr. Lyons and Dr. Gage were reported last year from New Orleans. I am certain that in the next few years the surgeon will extend his concern about the management of hemorrhage to the late effects of acute blood loss on the body tissues as a whole.

DR. WILLIAM C. WHITE, New York: I thought it would be interest to emphasize a couple of points in which we have become greatly interested at Roosevelt Hospital in New York. About a year and a half ago we had the problem of treating a case of massive hemorrhage that had been admitted to the medical service and kept there for ten days. He had been given 8000 cc of citrated blood. One of my associates operated on this case, was thoroughly satisfied with the procedure, but at autopsy three days later we found there had been no evidence whatsoever of repair of the tissues, although he felt that he had performed a meticulous excision of ulcer with pyloroplasty. We believed that the long wait plus the introduction of so much foreign blood had done something to the reparative power. For that reason, we have decided to operate within 24-36 hours or not at all, during the acute phase. We have become satisfied with this policy. For that reason, in agreement with the medical service, we have made it a practice to admit all massive hemorrhage cases to the surgical side.

We are in complete accord with what Dr. Stewart has said, but I would like to emphasize a factor which he perhaps did not have time to mention. We routinely use a thin barium by mouth in all these cases, even though they are extremely sick. We do not allow fluoroscopic pressure, as we are a little fearful of what might happen. If we cannot get any evidence of ulceration of the stomach or duodenum, we treat these cases in a palliative fashion.

DR. J. E. RHOADS, Philadelphia: I think we are all in agreement with the principle that many of these patients should be operated upon earlier than has been the case in the past, and that we should avoid having them carried along for many days in medical wards and then turned over for surgery practically in extremis. However, I wonder somewhat whether it is necessary to divide all this group of patients at once into those we are going to operate on immediately and those whom we are not going to operate on at all. It seems to me there is a good deal of experience to show that large numbers of these patients will stop bleeding spontaneously, and that they can be operated upon more safely after they have recovered from the immediate effects of hemorrhage. For that reason, many of us have felt it better to give most of them a chance to stop bleeding on a medical regimen. Admittedly, this increases the risk somewhat for those who will not stop bleeding, but after all, this group is in the minority. It should make the overall mortality lower because those who do stop bleeding will recover from the effects of the hemorrhage and can then be operated on in the interval, while those who do not stop bleeding can still be operated on after a trial period on a Meulengracht regime, with success in a large percentage of cases.

DR. GAVIN MILLER, Montreal: Massive hemorrhage in the older group gives a high mortality and multiple transfusions may tide these patients over the crisis but, as Dr. Churchill pointed out, they do not respond as well to further transfusions if a second crisis occurs, no matter how much blood is given. I am inclined to consider transfusions as a temporary assistance, but not to consider that a transfusion in all ways take the place of the blood lost. It is a foreign body, and given in too large quantities may overstep the margin of safety and cause damage. When skin grafts are used from parent to child as a temporary means of covering burned areas they "take" but do not live, and gradually disintegrate. I think that blood probably acts in a similar way when given to another person, and soon is destroyed. This is perhaps the reason for the marked secondary anemia which may be difficult to overcome after

prolonged hemorrhage. For 20 years I have advocated "immediate" operation; that is, if bleeding does not stop within 24 hours, on patients past 45 years of age who are admitted with massive hemorrhage. In this group of patients—who number 8 or 9—no fatality has occurred when the stomach was resected. Had those patients been allowed to bleed on for days, a higher mortality would have occurred, as all statistics on bleeding ulcer tend to show.

DR. CHARLES G. JOHNSTON, Detroit: Dr. Stewart's presentation seems to me to be a very timely one. We have treated these patients in the past expectantly, and all too often there is great difficulty in having surgeons see these patients early enough to follow them well or to treat them. In many institutions it is common practice for bleeding peptic ulcers to be admitted to the medical ward, and for the internist to call the surgeon only when he has failed completely, and in many instances the surgeon is called when the patient is practically moribund. Recently, with some difficulty, we have been able to have these patients admitted directly to surgery, and our experience with them has been much better. We have found, as I am sure most of you have, that an operation in the early stages with adequate replacement of blood at the time of operation, is a lot less likely to cause death than a similar operation two, three or four days later, after the patient has been bled out several times and has had frequent blood replacement. Dr. Stewart's discussion of this is very interesting to me.

When such a patient is admitted to our hospital he goes to the surgical ward. If he is bleeding from the upper gastro-intestinal tract a stomach tube is passed into the stomach, and the stomach is well washed out. One of my associates, Dr. Byrne Daly, has amply demonstrated that it is quite possible to keep the stomach alkaline enough by the administration of phosphate buffers to permit the action of thrombin. The stomach is washed out, the phosphate buffer is introduced, the tube is kept in place with light suction and then 10,000 units of thrombin is added. If the thrombin is going to work, it works very soon, and within an hour or two one can tell whether the patient is going to stop bleeding. If he continues to bleed we recommend, regardless of his age, that he be operated upon and usually a gastrectomy is performed. We have felt this to be much more in keeping with sound principles of surgery. If a patient were bleeding externally, a direct attempt would be made to stop it. It seems to me that it is quite difficult to tell what is happening or is going to happen to the patient if one does not know and cannot determine the amount of bleeding. We find it quite necessary to continue alkalization with the buffer solution for a fair period of time after bleeding stops. In the first cases we were not successful because, after the bleeding stopped, we stopped giving the buffer solution. We interpreted our failure as due to digestion of the soft clot which had been formed. It is quite obvious that thrombin will not stop bleeding in an open vessel of any size, but many patients bleed through smaller vessels and without a great deal of force, and many of them do stop after thrombin and buffer is given. Those that continue to bleed should receive early surgical treatment.

DR. JOHN D. STEWART, Buffalo (closing): I think you must have noted that, in the discussion, the time factor has been mentioned repeatedly. It seems to me that this is one of the crucial aspects of this question. A patient with massive bleeding from an ulcer of the upper gastro-intestinal tract is to be considered a surgical emergency. Certainly such patients should be admitted on the surgical rather than the medical service. The time factor is of utmost importance.

It used to be stated by the older surgeons, who based this on accumulated sound observation, that a patient who was bleeding massively from an ulcer would respond to one transfusion, possibly even two, but not to the third. That has been an interesting consideration to me. There are at least two explanations that come to mind. In the first place, undoubtedly one, two or three pints of blood under the circumstances

was inadequate replacement; but the second point, more interesting, is that during the course of massive hemorrhage and shifts of body fluids, a great many metabolic changes undoubtedly take place which have not been fully understood. It is not inconceivable that the enzymatic functions of the liver may be seriously disturbed by sublethal anoxia and precipitate irreversible changes. There is need therefore for early decision as to definitive treatment in these cases and that is one of the main points I want to bring out. In the selection of cases for early operative treatment various criteria have been advocated from time to time. I am doubtful of the value of such a policy for I do not believe it is possible to tell with any degree of assurance which patients will stop bleeding. I am particularly opposed to a "wait and see" policy, for during the period of procrastination irreversible changes in vital organs may occur and the opportunity to perform effective surgery may be lost. With respect to the age factor, statistically speaking older patients are unquestionably less tolerant of massive hemorrhage. However, some young patients die and some old patients survive. Our approach to date has been more in the direction of setting up an active plan of treatment which offers the best prognosis regardless of age.

# THE SURGICAL TREATMENT AND THE PHYSIOPATHOLOGY OF COARCTATION OF THE AORTA\*†

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COARCTATION OF THE AORTA belongs to the group of congenital cardiovascular malformations in which arteriovenous shunts are absent, and in which there is no cyanosis. Fortunately, diagnosis is not difficult in most cases if one recalls that there is usually hypertension in the upper part of the body and hypotension below. There is usually evidence of increased collateral arterial pathways in the upper part of the body, absence or suppression of arterial pulsations in the lower extremities, and notching of the ribs in the older patients. A systolic murmur may be present. The stenosis or atresia can usually be visualized by angiocardiography. The complications associated with severe coarctation include those accompanying hypertension due to other causes.

This paper consists of a consideration of the surgical treatment and the physiopathology of coarctation of the aorta. The surgical treatment will be considered first.

The first method for treating coarctation was published by Blalock and Park<sup>1</sup> in March, 1944, in a paper entitled "The Surgical Treatment of Experimental Coarctation (Atresia) of the Aorta." In brief, this method consisted of using the left subclavian artery as a pathway by which the blood could be shunted beyond the point of stenosis. The use of this method was not attempted on patients at this time, and in the latter part of 1945 Crafoord and Nylin<sup>2</sup> and Gross and Hufnagel<sup>3</sup> reported a better method. This consisted of excision of the stenotic area and the performance of an end-to-end anastomosis between the proximal and distal ends of the aorta. The first operation on a patient by Crafoord was on October 19, 1944, and that by Gross on June 28, 1945. Clagett<sup>4</sup> of the Mayo Clinic was the first to use the subclavian artery to by-pass the point of stenosis in patients.

Everyone is agreed that the ideal operation is one in which the stenotic area is excised and the proximal and distal ends of the aorta are united by suture. Unfortunately there are some instances in which this does not appear to be feasible. Most frequent among these are those cases in which the atretic area is long and those in which the aorta is so diseased that end-to-end suture following excision is not feasible. The question has been raised as to whether one should employ the left subclavian to by-pass the point of stenosis if the ideal operation cannot be performed. It is our contention that this method

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should be used providing one does not have to sacrifice the large intercostal collateral arteries which arise from the aorta just beyond the point of stenosis. It is usually possible to save these blood vessels. It is our impression that the transposed subclavian artery will convey more blood to the lower part of the body than will the collateral vessels from the undivided subclavian artery.

There are several points about the technic of the operation which are worthy of brief comment. The first of these is concerned with the incision. In some of the earlier operations the posterior half of the fifth rib was removed and the paravertebral ends of the fourth and sixth ribs were divided. We now follow the recommendation of Crafoord in removing practically the entire length of a rib, usually the fifth, and it is not necessary to divide other ribs. An adequate exposure is obtained and there appears to be less discomfort and dyspnea in the postoperative period. Furthermore, there is less damage to intercostal blood vessels.

In the earlier operations which we performed, one or more pairs of intercostal arteries immediately distal to the point of coarctation were doubly ligated and divided. With additional experience we now follow the advice of Crafoord in trying to spare these arteries. In the first place these vessels are very large and thin walled, and one may encounter troublesome bleeding as a result of attempted ligation and division. In the second place these arteries are important collateral pathways, and it is particularly important to preserve them in case difficulty should be encountered in completing the anastomosis. The intercostals just distal to the coarctation may be occluded with one or more rubber-shod clamps. Fortunately, these vessels run upwards and do not interfere with approximation of the ends of the aorta while the anastomosis is being performed.

In the majority of patients with coarctation of the aorta the point of stenosis is only a short distance beyond the point of origin of the left subclavian artery. Obviously one can occlude the left subclavian artery as well as the aorta during the time required for excision of the stenotic area and the performance of an end-to-end anastomosis, but this decreases the quantity of blood which reaches the lower part of the body during this procedure. We have been able to escape this added danger by using a modified Potts arterial clamp which occludes the aorta completely, but permits some circulation through the subclavian artery. This clamp is introduced in the free space between the points of origin of the left common carotid and the left subclavian arteries. It is shown in place in Figure 1.

A single layer of sutures which includes the entire thickness of the wall of the aorta has been used in our operations and in those by Gross. This point is mentioned because Crafoord has attempted to avoid inclusion of the intima of arteries in his anastomoses. It is our opinion that one obtains a smoother intimal surface and a stronger arterial wall with less tendency to the formation of aneurysms when the entire thickness of the wall of the vessel is included in the suture.

It is probably a matter of personal choice as to whether one employs an everting or an overhand suture in performing the anastomosis. We prefer the former type because it leaves less suture material and smoother intimal surfaces in contact with the flowing stream of blood. The suture material which we use is 0000 silk on small round needles (Deknatel).

Following the completion of the anastomosis, we have followed the advice of Gross in releasing the occlusion of the aorta slowly and at the same time lowering the patient's head and introducing blood intravenously rather rapidly. In one patient the heart's action became slow and feeble but it improved on reapplication of the clamp. Subsequent removal of the clamp was tolerated without incident.

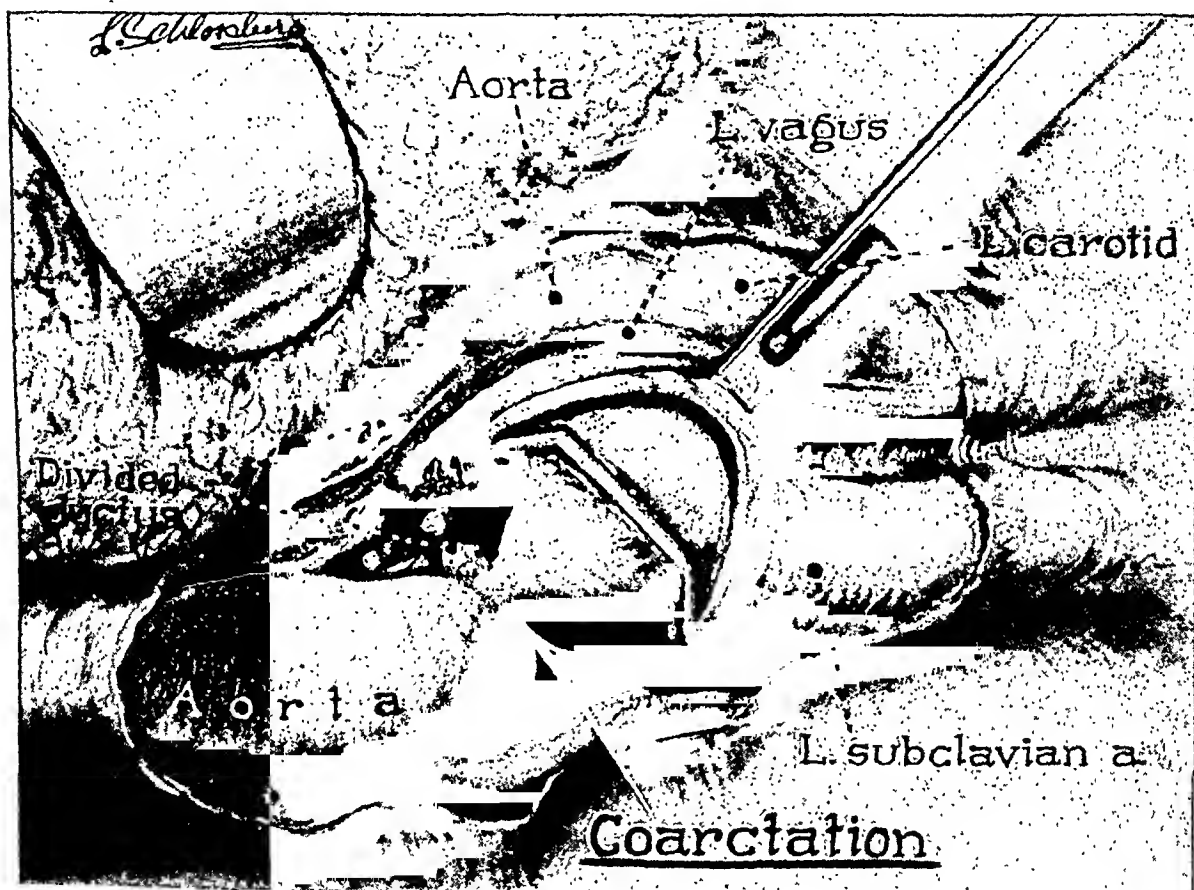


FIG. 1.—Illustrates the modified Potis clamp in position. It may be seen that while it occludes the aorta completely, it permits blood to flow through the subclavian artery.

Our operative experience is limited to 23 patients with coarctation of the thoracic aorta. The ages varied from 7 to 31 years. Thirteen of the patients were 20 or more years of age. An anastomosis was attempted in 22 of the 23 cases and was completed in 21 of them. In the one case in which the anastomosis was not attempted the site of coarctation was several interspaces below the usual site and the constriction was longer than usual. Furthermore, the distal aorta was somewhat hypoplastic and was surrounded by adhesions. In the case in which the anastomosis was attempted but not completed, the proximal aortic clamp became dislodged, resulting in sudden stoppage

of the heart after approximately one pint of blood had been lost. Even though control of the vessel was obtained quickly, efforts at resuscitation failed. As a result of this experience, a mechanism for locking the aortic clamps was devised.

An anastomosis was completed in 21 of the 23 cases. In 17 of these the site of coarctation was excised and an end-to-end anastomosis was performed between the proximal and distal ends of the aorta. The only fatality in this group was a 13-year-old boy in whom a cerebral thrombosis of the left internal

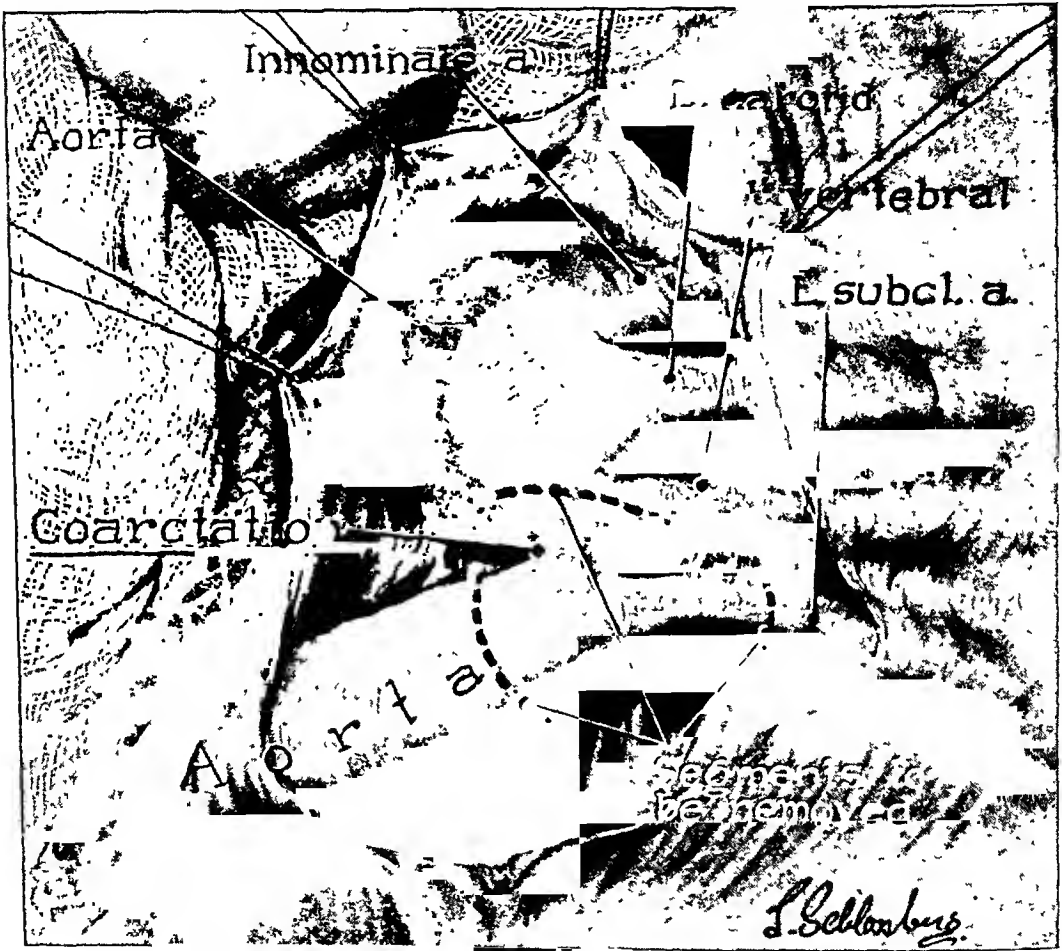


FIG. 2.—Reveals the findings in a patient in whom the subclavian artery arose distal to the point of stenosis.

carotid and left middle cerebral arteries occurred postoperatively. It was noted preoperatively that he stuttered quite badly. The operative procedure was an easy one and no difficulty was encountered. The only other complication in this group was the development of a sixth cranial nerve paralysis on the right in a recent patient. It was felt that this may have been caused by a pre-existing intracranial aneurysm.

In four patients the proximal segment of the aorta was considered to be too short for an end-to-end suture, and the left subclavian artery was used

to by-pass the point of stenosis. Most of these cases occurred in the early part of the series and it is likely that with additional experience an end-to-end anastomosis could have been performed in some of them. There was one death in this group. The patient was a child of seven who had evidence of heart failure with pulmonary hypertension preoperatively. Free pleural fluid and pulmonary edema were present at the time of operation. The anastomosis was performed without difficulty but the child died as the chest was being

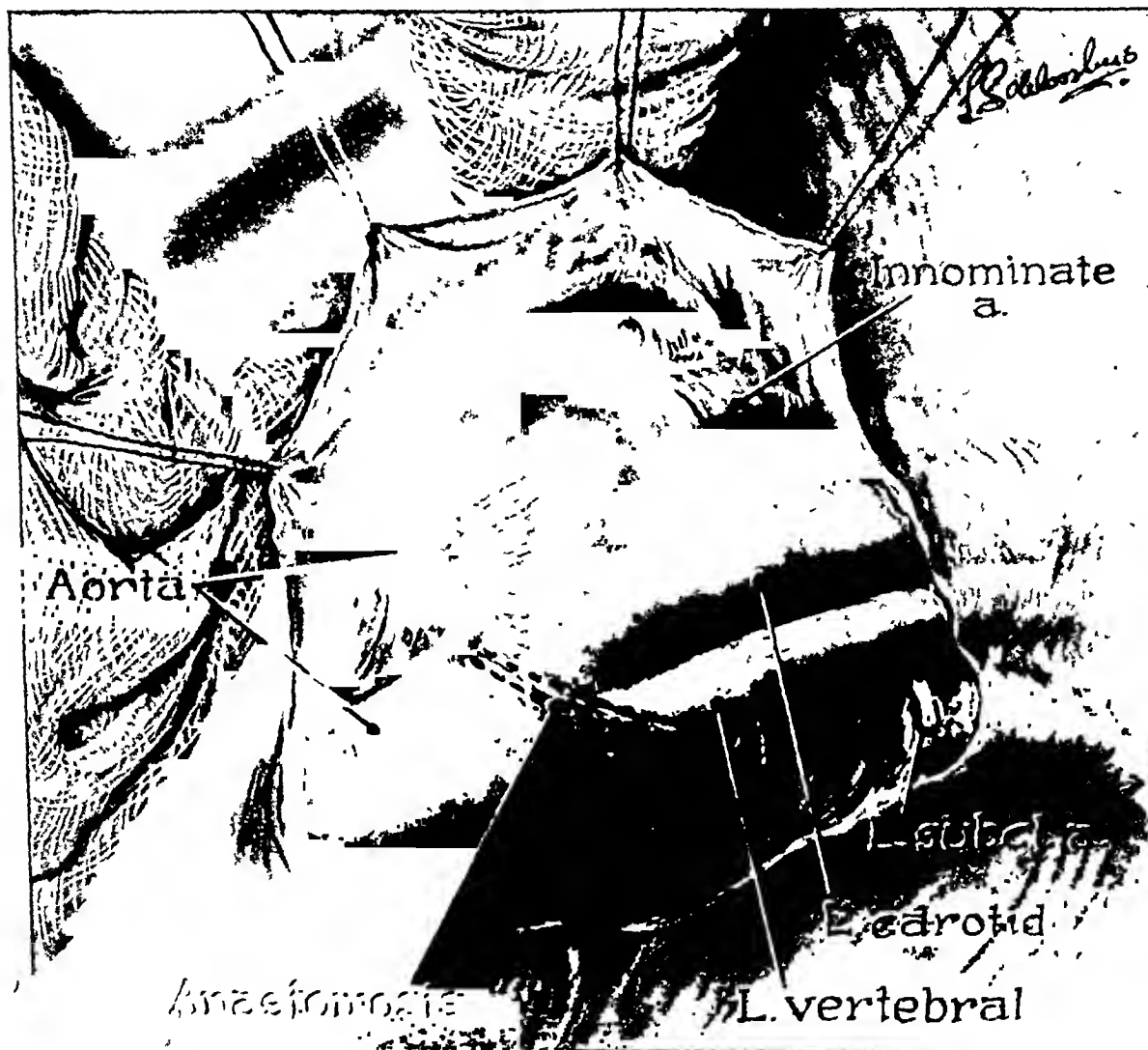


FIG. 3.—Shows the completed anastomosis. It may be seen that the subclavian artery has been divided, and that the suture line extends onto the base of the vertebral artery.

closed. Mitral stenosis, thickening of the tricuspid valve, pulmonary arterio- and arteriolar sclerosis, and pulmonary edema were found on postmortem examination. A second patient in this group developed a partial paralysis of the legs as a result of the operation. It was the opinion of the consulting neurologist that this was due to an occlusion of the anterior spinal artery which may have been aberrant.

If we consider the two groups together, it is to be observed that there were three deaths in the 22 cases. Two of these occurred in the younger age group



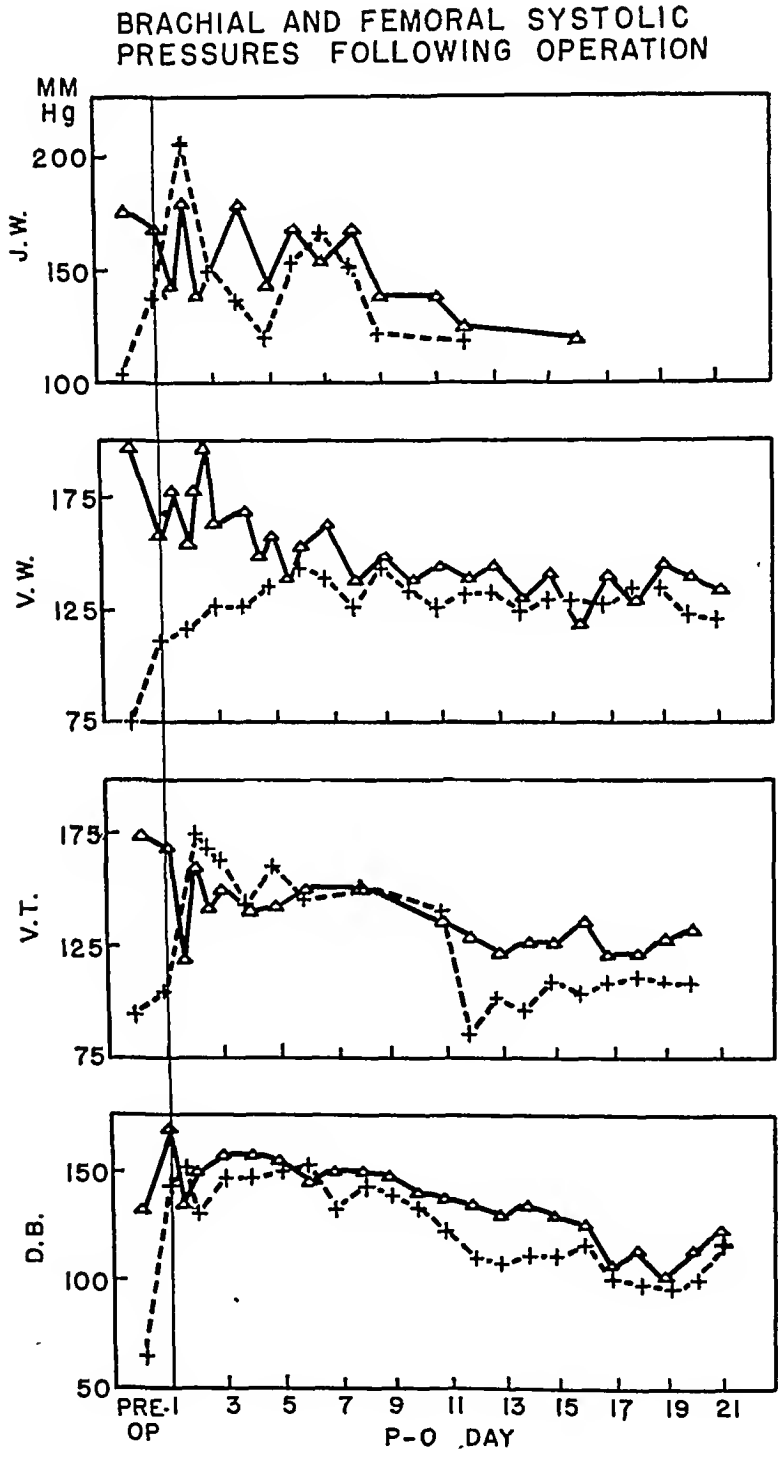


FIG. 4.—Charts the changes in blood pressure following resection of the stenosis. The solid line represents brachial systolic pressures; the broken line femoral systolic pressures.

and one in the older. The latter death was due to a technical error at the time of operation and should have been avoided. Cerebral thrombosis in one case and pulmonary edema in the presence of valvular disease and pulmonary sclerosis in the other accounted for the two deaths in the younger age group.

The findings in one of the cases were of sufficient interest to merit specific comment. Physical examination and angiocardiology in a female of 26 indicated that the coarctation was proximal to the orifice of the left subclavian artery. Arterial pulsations in the left arm were weaker than those in the right, and notching of the ribs was present on the right and not the left. On exploratory thoracotomy it was found that the left subclavian artery arose from the aorta immediately distal to the point of stenosis. Temporary occlusion of this artery did not cause a diminution in the radial pulse on the left; in fact, the anesthetist thought it caused the pulse to become stronger. The flow of blood in the left subclavian artery was the reverse of the normal direction. The orifice of the left subclavian was so close to the site of coarctation that it appeared to be necessary to sacrifice it in doing an excision of the stenotic area and an end-to-end anastomosis. A diagram of the operative procedure is shown in Figures 2 and 3. A satisfactory result has followed this operation.

During the three weeks postoperative period that our patients have remained in the hospital, two observations have been made which seems worthy of comment. In every case where headache has been a prominent preoperative symptom, it has been conspicuously absent postoperatively. It has also been noted that the systolic blood pressure in arm and leg require some five to ten days to stabilize. This is illustrated in Figure 4, and has been commented upon by Gross<sup>5</sup> and Shick.<sup>6</sup> Follow-up studies upon these patients are currently in progress.

Studies on the *physiopathology* of this malformation have dealt primarily with the etiology of hypertension in the upper part of the body. Therefore, most investigators have been concerned with the relationships of blood pressures, blood flows, and vascular resistance in the upper and lower extremities. Conclusions drawn from the studies have been controversial. Blumgart found normal arteriolar pressures in the arms and legs and concluded that the elevation in blood pressure was the result of the resistance offered by the aortic stricture and the collateral pathways.<sup>7</sup> Similar conclusions were reached by Lewis, who found normal blood flow through the arm and leg, but observed vasodilatation in the head, neck, and hand.<sup>8</sup> More recent studies, however, have emphasized the role of peripheral arteriolar resistance. Pickering postulated an increase in arteriolar resistance limited to the upper part of the body and attributable to vascular narrowing.<sup>9</sup> Prinzmetal and Wilson found decreased blood flow through the arm and concluded that arterial hypertonus of vasomotor origin must be present in the upper limbs.<sup>10</sup>

The introduction of intra-arterial blood pressure measurements in man by Hamilton's method opened a new line of approach.<sup>11</sup> Using this technic, Steele

found elevations above normal of the diastolic pressure in the radial and femoral arteries. This was interpreted as evidence of a generalized increase in arteriolar tone throughout the body.<sup>12</sup> According to Rytand, interference with the renal blood supply caused by the stricture of the thoracic aorta was responsible for the increased resistance.<sup>13</sup> This conclusion was supported by the finding of Goldblatt that hypertension occurred if the aorta was constricted

## CARDIAC INDICES

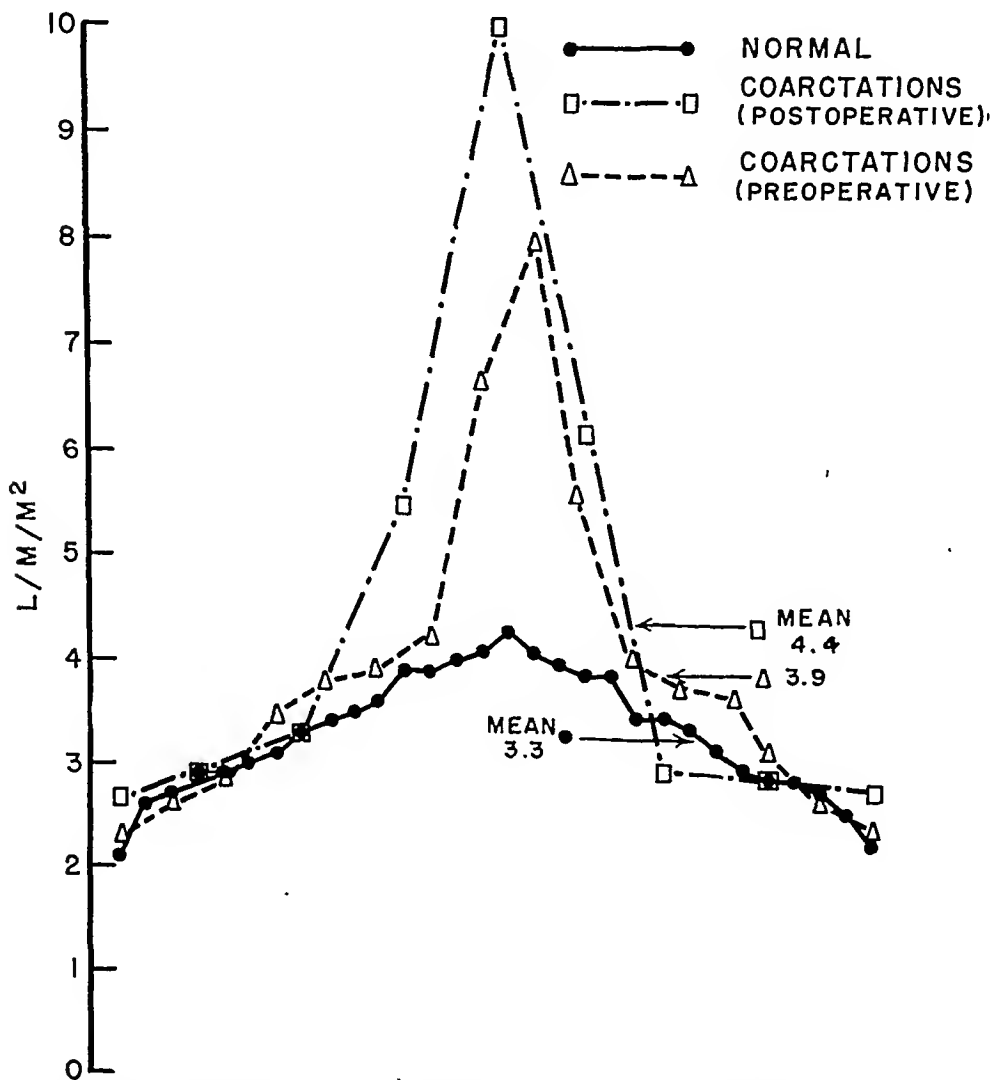


FIG. 5.—Illustrates the cardiac indices of normal individuals as well as patients with coarctation of the aorta both pre and postoperatively. It may be seen that the cardiac indices show no significant deviations from normal values.

above the level of the renal arteries and failed to appear when the aorta was constricted below.<sup>14</sup> Increased renal vascular resistance, observed in cases of coarctation of the aorta, might be construed as further evidence of the participation of the kidney in the production of hypertension.<sup>15</sup> On the other

hand, hypertension in the arm has been observed in several cases of coarctation where the stricture was below the level of the renal arteries. In one of these the renal blood flow was normal.<sup>16</sup>

This short review of the literature illustrates the variety of results and interpretations. The introduction of surgical therapy is of such recent date

ARM BLOOD FLOWS

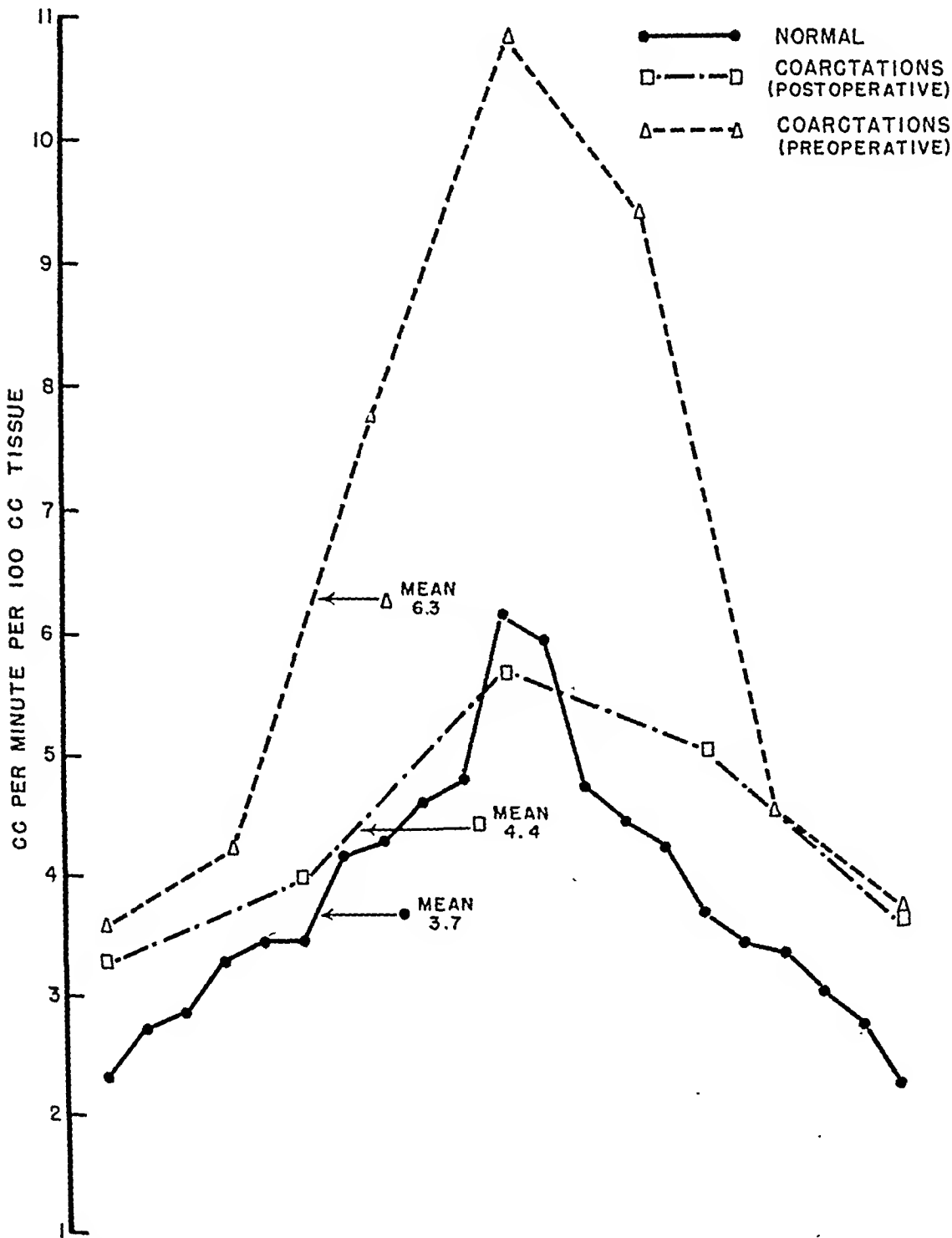


FIG. 6.—Shows that the mean preoperative blood flow through the forearm of patients with coarctation is markedly elevated. Postoperatively it falls to essentially normal levels.

that few reports dealing with postoperative changes have been published. The succeeding paragraphs of this paper deal with studies concerning the pre- and postoperative hemodynamics in coarctation. The mechanisms leading to hypertension will be discussed in the light of these findings.

A total of 22 patients were studied. Postoperative investigations were carried out three weeks following surgery. Cardiac output was determined according to the Fick principles using right heart catheterization for sampling of mixed venous blood.<sup>17</sup> All cardiac outputs were expressed in liters per minute per square meter of body surface (cardiac index). Blood gas analyses

## LEG BLOOD FLOWS

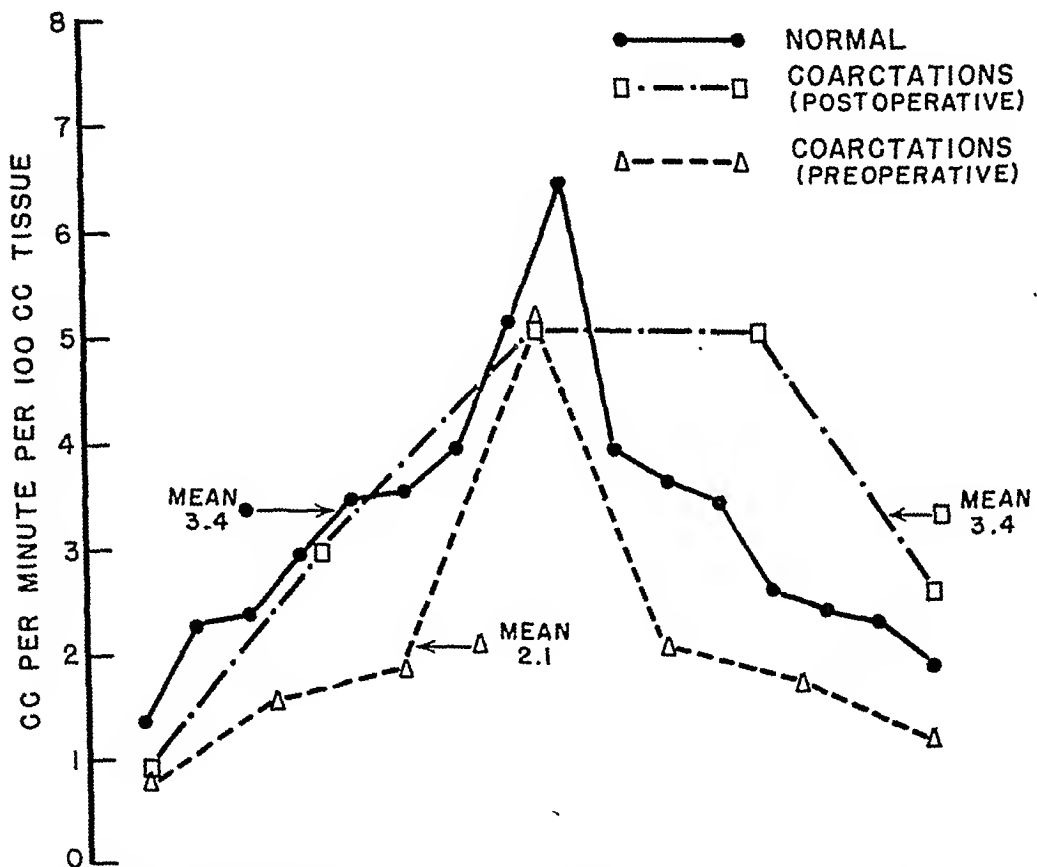


FIG. 7.—Illustrates that the mean preoperative blood flow through the calf is slightly below normal values, rising postoperatively.

were carried out in the manometric apparatus of Van Slyke and Neill.<sup>18</sup> Analyses of respiratory gases were performed using the apparatus of Haldane<sup>19</sup> and the Pauling oxygen analyzer. Intra-arterial blood pressures were determined using hypodermic strain gauge (Statham) or Hamilton manometer.<sup>11</sup> Mean pressures were derived by planimetric integration of the area under the pressure curve. Renal blood flow and glomerular filtration rate were determined in most of these individuals by Dr. Jacques Genest and co-workers using the

clearances of para-amino hippuric acid and sodium thiosulfate. Their studies form the subject of a separate report, but reference will be made to their results. Blood flows through the leg and forearm were measured at 32° C. with the plethysmograph described by Wilkins and Eichna.<sup>20</sup> Their results on 14 normal individuals agreed closely with those obtained on five normal individuals in this laboratory. The combined data were used in the statistical evaluation of normal blood flows through the forearm and leg. There is considerable disagreement in the literature concerning values for normal blood flow through the extremities.<sup>8, 12, 20</sup> This appears to be primarily the result of differences in the apparatus used and of variations in the temperatures at which determinations were made.

#### COMPARATIVE PRE AND POSTOPERATIVE BLOOD PRESSURES

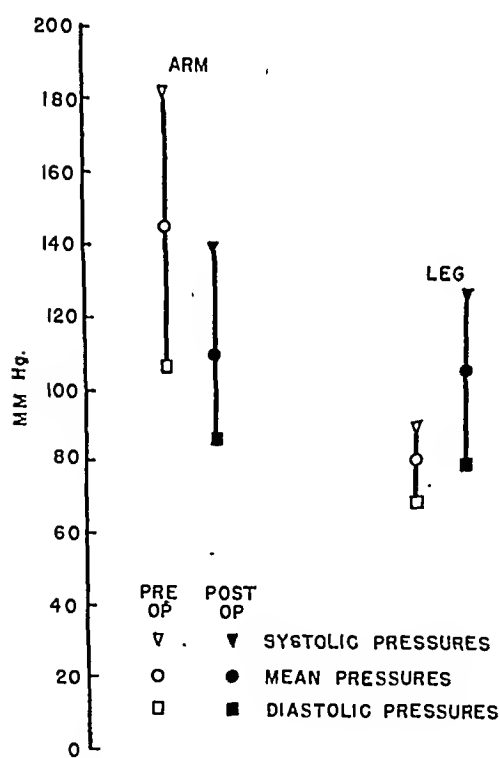


FIG. 8.—Shows the relationship of intraarterial systolic, diastolic, and mean pressure in arm and legs pre and postoperatively. It may be seen that after operation pressures tend to equalize.

Figure 5 illustrates the preoperative cardiac indices of 16 individuals; in nine, the indices were determined postoperatively. It may be seen that there was some scatter of the figures. In three instances the pre- and postoperative values for cardiac outputs were significantly elevated above normal. However, the remainder of the data fell within the normal range established by Cournand and his associates. (Fig. 5.)<sup>21</sup> It may be concluded, therefore, that the cardiac output of patients with coarctation of the aorta before and after resection of the stenosis is within normal limits.

The blood flow through the forearm was determined preoperatively in seven cases. Postoperative observations were made in five individuals. Figures 6 and 11 illustrate that the preoperative blood flows through the arm were sig-

nificantly elevated above normal, with a mean value of 6.3 cc./min./100 cc. arm tissue, as compared with a normal of 3.7 cc. Postoperatively the blood flow through the forearm decreased toward normal. (Figs. 6 and 11.) In contrast, the preoperative blood flow through the calf, determined in the same individuals, was below the standard deviation of the normal, with a mean of 2.1 cc./min./100 cc. leg tissue as compared to 3.4 cc. in the normal. (Figs. 7 and 11.) Postoperatively the flow through the calf, measured in five cases, rose to normal levels. These findings are at variance with those obtained by

Lewis, who found normal blood flows in both upper and lower extremities.<sup>8</sup> Low flows through the arm and hand were described by Prinzmetal and Wilson.<sup>10</sup> It is probable, however, that the results are not comparable because of the variations in the techniques.

Direct intra-arterial blood pressure determinations from the brachial and femoral arteries were performed in 17 preoperative cases. (Fig. 8.) In seven of these, pressures were recorded simultaneously. (Fig. 9.) Figure 9 shows the elevation of the systolic and mean pressures in the arm.\* With two excep-

SIMULTANEOUS PRESSURE RECORDINGS  
IN COARCTATION OF THE AORTA . .

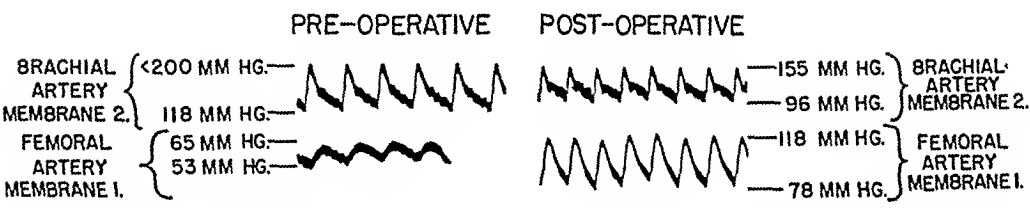


FIG. 9.—Is a simultaneous direct pressure recording from the brachial and femoral arteries before and after operation.

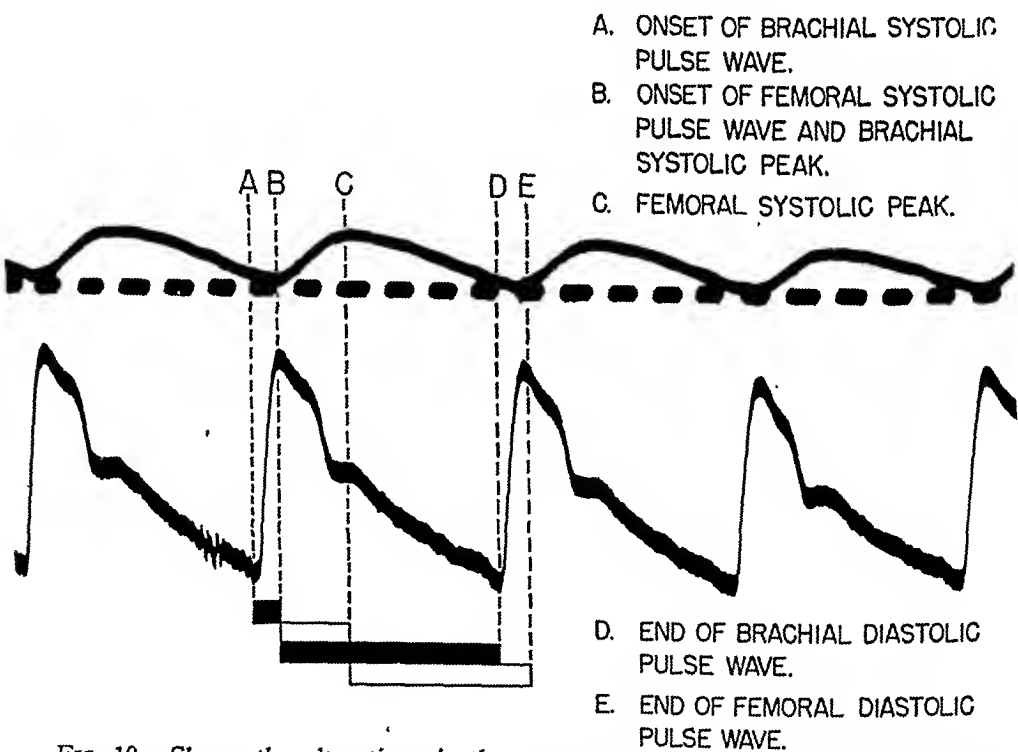


FIG. 10.—Shows the alterations in the components of the femoral pulse wave as compared with the brachial pulse wave. The delay in the onset of the femoral upstroke, and the difference in duration of brachial and femoral upstrokes in demonstrated.

\* Following the criteria of the American Heart Association, the upper limit of normal systolic pressure was taken as 140, the upper limit of normal diastolic pressure was taken as 90 mm. Hg. The upper limit of normal mean pressure was considered to be 110 mm. Hg.

tions, the diastolic component was also elevated. The pulse pressure was increased. Postoperatively the systolic, diastolic and mean pressures fell in most instances. (Fig. 8, Table I.)

The systolic blood pressures taken from the femoral artery of 15 individuals were below normal in every instance. In only one patient was the diastolic pressure higher than normal. Mean pressures were not elevated. Postoperatively, the systolic and mean pressures rose, the diastolic component remaining almost constant. (Fig. 8.) These findings corroborate those of King, Steele, Gross, and others.<sup>22, 12, 5</sup>

The contours of the femoral and radial pulse waves have been compared by Woodbury and by Brown and their associates.<sup>23, 24</sup> These investigators found the brachial pulse contour of normal appearance. Pressure curves from the

TABLE I.—*Direct Blood Pressure Determinations in Coarctation*

Name	Preoperative				Postoperative			
	Arm		Leg		Arm		Leg	
	S/D mm. Hg	Mean	S/D mm. Hg	Mean	S/D mm. Hg	Mean	S/D mm. Hg	Mean
E. W.	205/122	150	105/89	97				
A. W.	196/107	136	98/80	91	157/77	98	154/92	122
M. O.	133/103	114	115/98	103	112/65	88	147/85	106
B. C.	200/115	162						
W. D.	171/93	135	125/52	91			148/90	110
H. S.	186/118	170	102/78	87			109/72	88
C. S.	150/38	142	88/66	77	160/140	147	89/72	78
D. P.	>200/134	173	78/62	72	120/75	91	125/74	87
W. B.	>200/118	174	65/53	61	155/96	128	118/78	93
C. C.	150/107	132						
B. A.	>200/100	144	52/45	48				
V. W.	200/97	170	68/52	63	124/84	104	109/73	88
J. W.	178/91	144	100/77	92	144/71	96	112/66	88
R. K.	200/92	162	96/73	88	178/98	140	178/102	140
V. T.	175/88	127	97/74	84	134/70	108	142/73	125
A. P.	>200/100	160	91/61	78				
D. B.	134/62	98	66/52	62	122/71	92	108/58	79
Arith. Mean	>183/106	144	91/68	81	141/85	109	128/78	100

femoral artery, however, showed a retardation of the upstroke of the pulse wave and a broad rounded peak, making the pulse contour almost a smooth curve. Figure 10 illustrates the contrast between the configuration of the brachial and femoral pulse waves in a patient of this series. The shape of the femoral pulse wave is the result of damping of each wave as it passes through the area of resistance presented by the aortic stricture and the collateral channels. It has been pointed out that the effect of the insertion of a small to moderate resistance into the pathway of a transmitted wave is to dampen the amplitude of the curve, leaving the mean pressure relatively unaffected.<sup>25</sup> It is by this mechanism that femoral pulse pressure is reduced while mean pressure remains at or near normal levels.

Prolongation of the normal interval between the onset of the upstroke of the femoral and the brachial pulse waves has also been reported.<sup>23</sup> Similar observations were made in the patients of this series. It may also be seen in Figure 10 that the duration of the femoral arterial upstroke was more than



twice that of the brachial. Since the sum of the entire length of the pulse wave is the same for both brachial and femoral arteries, the downstroke component must be shortened in the femoral.

*Analysis of the physiologic data.* An analysis of the mechanisms of hypertension from the data presented must deal primarily with the relationship of vascular resistance, blood flow, and blood pressure. Since the cardiac output of patients of this series is normal, the hypertension must be due to an increase in vascular resistance. This could be the result of one of two mechanisms. The first mechanism was suggested by Blumgart, who believed that the site of resistance was in the aortic stricture and collateral vessels.<sup>7</sup> The second mechanism, proposed by Steele,<sup>12</sup> by Stewart,<sup>26</sup> and by Rytand,<sup>13</sup> postulated that the increase in resistance was generalized, affecting the whole peripheral vascular tree. Such a disturbance exists in renal and in essential hypertension. Rytand is of the opinion that in coarctation the kidney is responsible for the increased resistance because of interference with its blood supply.<sup>13</sup> If this were the case, the overall arterial resistance exclusive of the stenosis and the collaterals should be elevated. However, calculation of an increase in overall peripheral resistance is not in itself sufficient evidence of a renal pressor mechanism, for in renal hypertension the resistance must also be equally distributed. By contrast, the increase in overall resistance which may be present in neurogenic hypertension produced by sectioning of the buffer nerves in dogs is of unequal distribution.<sup>27</sup> Therefore, if the hypertension in coarctation is renal, the increase in arterial resistance must affect all branches of the circulatory tree to an equal degree.

The resistance due to peripheral arterial tone alone may be estimated by subtracting from the total overall resistance a calculated value for the resistance of the stenosis and the collaterals. Let  $rc$  represent the resistance through the collaterals and the coarctation;  $R_T$ , the total overall resistance; and  $RP$ , the resistance due to peripheral arterioles alone; then

$$(1) \quad RP = R_T - rc$$

With a simplified version of Poiseuille's formula  $\left( \text{Resistance} = \frac{\text{Pressure}}{\text{Flow}} \right)$

the various resistances may be estimated.\*

$$(2) \quad rc = \frac{PL}{F}$$

where  $rc$  represents the resistance through the collaterals and the coarctation;  $PL$ , the loss in pressure head across the coarctation and the collaterals; and  $F$ , the blood flow through the coarctation and the collaterals. Since it is not possible to ascertain the blood flow through this region, let  $F$  equal cardiac output. The  $rc$  thus derived then should be the lowest possible resistance for this portion of the vascular bed. Thus,  $R_T$ , the total overall resistance, would

\* All resistances calculated by these formulae are expressed in arbitrary units.

represent the highest possible value, and RP would likewise be maximal.

$$(3) \ R_T = \frac{PA}{F}$$

where  $R_T$  represents the total overall resistance, including that of the coarctation and the collaterals, PA the mean pressure in the brachial artery, and F equals the cardiac output.

Table II illustrates that preoperative and postoperative values for the peripheral resistance exclusive of the stenosis and the collaterals are below normal. Since these values are maximal, true peripheral resistances must be

TABLE II.—*Peripheral Resistance in Coarctation of the Aorta*

Case	Preoperative			Postoperative		
	$R_T^*$	rc*	RP*	$R_T^*$	rc*	RP*
B. A.	39	26	13			
V. W.	41.5	26	15.5	38.5	6	32.5
J. W.	49.5	18	31.5	17.5	1.5	16
R. K.	38.5	17.5	21	14	0	14
V. T.	33.5	11	22.5	36	0	36
A. P.	24	12	12			
D. B.	26	9.5	16.5	33	4.5	28.5
MEAN			19			25
NORMAL*			29			29

\* $R_T$  = total resistance including stenosis and collaterals = brachial pressure/cardiac index.

rc represents the resistance of the stenosis and collaterals =  $\frac{\text{drop in pressure}}{\text{cardiac index}}$ .

$R_p$  represents the peripheral resistance =  $R_T - rc$ .

Normal peripheral resistance calculated using a mean pressure of 96 mm. Hg and a cardiac index of 3.3.

lower. This finding differentiates the mechanism of hypertension in coarctation from that in renal and essential hypertension.

Further evidence for the absence of a renal mechanism in the pathogenesis of hypertension in coarctation is lack of proportional increase in resistance in various portions of the vascular tree. In an attempt to assess the resistance in various parts of the body, Steele<sup>12</sup> and Stewart<sup>26</sup> postulated an increase in the arteriolar resistance of the leg on the basis of an elevation of the diastolic pressure in the femoral artery. A similar increase in resistance was demonstrated in patients of this series despite the finding that only one out of 15 preoperative cases showed an increase in femoral diastolic pressure. This calculated increase in resistance accounts for the decrease in blood flow through the leg in the presence of a normal mean pressure. It is apparent from preceding discussions that conclusions regarding peripheral vascular resistance drawn from the height of the diastolic pressure alone are unjustified.

It is of interest that following the operation the blood flow through the leg approaches normal. (Figs. 7 and 11.) During the postoperative period of observation, however, there is a proportional rise in the mean pressure in the femoral artery, indicating that the postoperative resistance in the leg remains elevated. (Fig. 11.)

Blood pressures from the brachial artery obtained in the patients of this series agree with those of King, Steele, and others.<sup>22, 12</sup> Figure 9 illustrates that brachial systolic, diastolic and mean pressures are elevated. The blood flow through the arm is markedly increased (Figs. 6 and 11), and consequently the mean resistance is normal or only slightly elevated. (Fig. 11.) On the other hand, in patients with essential and renal hypertension the arm flow is normal but the vascular resistance in the extremity is markedly elevated. Postoperatively the blood flow through the arm and the brachial arterial pressure decrease in the same proportion. Therefore, no appreciable change in the vascular resistance occurs.

There is general agreement that the vascular resistance in the kidney is increased in patients with coarctation.<sup>28</sup> As in essential and renal hyperten-

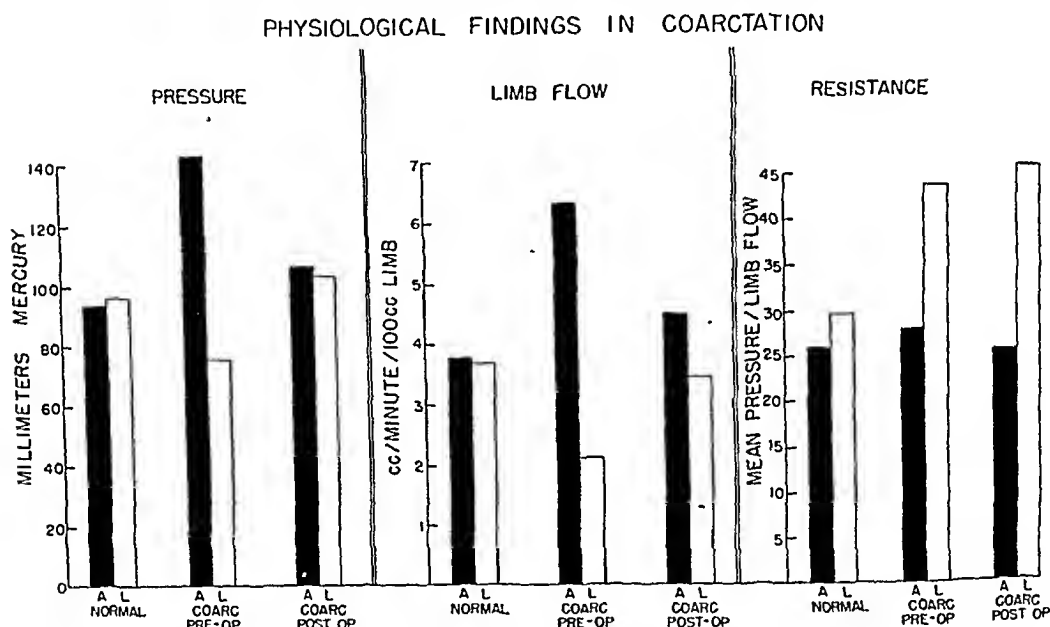


FIG. 11.—Compares mean pressures, blood flows through the limbs, and vascular resistance through the limbs before and after operation.

sion, the increased vascular tone is in the efferent arterioles. On the other hand, cases with severe hypertension in the upper extremity have been reported in which the coarctation was below the level of the renal arteries. In one of these, studied and explored at this hospital, the renal blood flow and the glomerular filtration rate were normal, but the vascular resistance in the leg was increased.<sup>16</sup>

Several findings in this report cast doubt on the theory that the hypertension in coarctation is the result of an increase in the peripheral resistance mediated through renal mechanisms. Estimated values for the overall arterial resistance exclusive of the coarctation and the collaterals are below normal. Furthermore, the existing peripheral resistance is unequally distributed. Since the resistance in the extremities is not lowered, other parts of the vascular bed must accommodate an increased blood flow. Investigations are in progress to determine the site of lowered vascular resistance. Finally, the increase in

the height of the diastolic pressure observed in both the upper and lower extremities, which has been used as evidence for increased arteriolar tone, can be readily explained as a result of damping of the pulse wave by the coarctation and the arterial collaterals.

#### SUMMARY

Twenty-three patients with coarctation of the thoracic aorta have been operated upon.\* Thirteen of the patients were 20 years of age or above, while ten were younger. An anastomosis was completed in 21 cases of the 22 in which it was attempted. In 17 cases the stenosis was resected and an anastomosis of the proximal and distal ends of the aorta was performed. In four cases in which the proximal segment of the aorta was too short for end-to-end suture, the left subclavian artery was used to by-pass the stenosis. There were three deaths in the series, including one in a child who had multiple congenital defects which had been recognized preoperatively.

Physiologic investigations disclosed no significant deviation of the cardiac output from normal. Blood flows through the arm, which were elevated before operation, fell following surgery. The blood flow through the leg rose postoperatively. Hypertension in the upper part of the body and hypotension the legs was observed preoperatively. After operation, these pressures tended to equalize. Analysis of the physiologic data indicated no generalized elevation of peripheral vascular resistance. It is probable, therefore, that the hypertension in coarctation of the aorta is not attributable to a renal pressor mechanism, but is due to the resistance of the stenosis and collaterals.

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\* Seven additional patients with coarctation of the aorta have now been operated upon. End-to-end anastomosis was carried out in all these patients and there were no additional deaths. Of these seven patients, one was 41 years of age.

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DISCUSSION.—DR. CLARENCE CRAWFORD, Stockholm, Sweden: First of all I should like to express my gratitude for the opportunity of being present at this meeting and taking part in this discussion, which I feel is a great honor. From the excellent results we have just heard from Dr. Blalock and his co-workers, and from my own experience, I think we may state that radical treatment of coarctation of the aorta can no longer be considered as a surgical equilibristic procedure; I think it can be said that it is a sound surgical procedure. The results I have had support the conclusions which can be drawn from Dr. Blalock's presentation.

We have now operated on 32 cases of coarctation; 31 of those were resected and

in one case we did a "Blalock operation" with anastomosis, end-to-side, between the subclavian artery and the aorta below the coarctation. In this series of 32 cases we had two postoperative deaths, one due to acute bleeding on the afternoon of the day of operation, the other due to formation of a dissecting aneurysm which broke into the bronchial tree, for the patient died a month after operation because of massive hemoptysis.

In addition to the 32 cases operated upon, we have explored five cases intending to try radical operation, but conditions were such that an anastomosing operation was not possible. These cases were in the older age group, between 25 and 35 years of age. In all, arteriosclerotic changes of the walls of the arteries were present, which made surgical intervention on the vessels impossible. In that group of five cases, which were explored and sutured again, we had two deaths shortly after operation. Because of that I would like to point out the value of a method of investigation that we have developed recently in the attempt to make as accurate an anatomic diagnosis of the lesion as possible before operation. We have introduced an ordinary cardiac catheter through the radial artery, pushing it forward down into the aortic arch. With the rapid injection of 50 to 70 cc. diodrast we can get an excellent x-ray picture of the first part of the aorta and the coarctation. I hope that, as we become more familiar with this method of investigation, we may be able to exclude most of the unsuitable cases from exploratory thoracotomy and select in advance those on which we may hope to achieve a good result.

(slides) In this picture you can see the catheter passed down into the arch of the aorta to the level of the aortic ostium. The curved outlines of the aortic valves are shown, and also a fairly good picture of the coronary arteries. We hope in the future to be able to carry out studies on the coronary arteries by this means. In the cases on which this procedure has been carried out, we have had no reaction which would contraindicate continuance of the method.

The second slide shows a case which was rather difficult to interpret. It was one of the first upon which this investigation was done, and we did not know how to interpret the different shadows. We therefore explored to confirm our x-ray findings, and in this drawing is shown what was found. There were multiple aneurysms on the aortic arch which made radical procedure of any sort impossible.

We have been able to follow 27 of the 32 cases for a period ranging between three months and three and a half years. Of the remaining five, two died in the immediate postoperative period, as mentioned, and three have been operated upon so recently that it is too early to tell how they will progress. In 13 of the 27 cases the blood pressure has returned to normal, with higher pressures in the legs than in the arms. In six, the blood pressure is equal in the legs and the arms and, in eight, it is still slightly higher in the arms than in the legs. In these eight we have not been able, from an anatomic viewpoint, to perform a sufficiently wide anastomosis.

In three cases of the 30 surviving there has been development of small postoperative dissecting aneurysms, demonstrated by direct aortagraphy after operation. Two of the three are symptomless; they have not been growing. In one case there are signs of increase in the size of the aneurysm, the patient has symptoms and we are discussing the possibility of reoperation.

The principal difference between the technic described by Blalock and Gross and the one I use is that both Blalock and Gross use everting sutures. I have felt that one should try to resect as much as possible of the constricted area, which is nearly always so long that it is difficult to resect enough. Because of that, I have used an anatomic suture with coaptation of the different layers of the aortic wall against each other, which permits resection of a few millimeters more than if an everting suture is used. I also feel that healing will be better and stronger when the different anatomic layers of the aorta are in direct contact. I do not know whether Dr.

Blalock and Dr. Gross have had postoperative aortagraphs made, or if they have found any postoperative symptomless aneurysms. A comparison between our series in that respect might give some indication as to whether the anatomic or the everting suture is to be preferred.

The mean blood pressure before operation in my cases has been 180/100 in the arms and about 100 mm of mercury systolic in the legs. After operation, the pressure in the arms has returned to normal, as mentioned above.

DR. EGBERT H. FELL, Chicago: I am sure we all appreciate this most extraordinary discussion by Dr. Crafoord. We all realize the great contribution made by Dr. Blalock and the impetus he has given to this new field of surgery. After spending a good deal of time in the laboratory and in attempting to operate on these cases, one realizes the great problems surmounted by Dr. Blalock, by our two new members, Dr. Gross and Dr. Potts, and by Dr. Crafoord, and it is their unselfishness and graciousness that has made it possible for those of us who are interested in the subject to carry on as we could not have done otherwise.

The purpose of this discussion is to present two cases to emphasize the fact that the most desirable time for operation is in childhood; first, because it is technically much easier and, second, because there are few or no irreversible reactions taking place in a child. Following such surgical procedures, these patients with very dark futures should be converted into normal or nearly normal individuals.

(slides) In the Presbyterian Hospital laboratories the technic as described by Gross was first carefully carried out in dogs. The success of these experiments encouraged us to attempt the procedure for the benefit of the boys to be described. These two children presented themselves in the pediatric cardiac service at Cook County Hospital about the same time for study. After Dr. Benjamin M. Gasul and his associates had completed their studies, they were transferred to the surgical service. The boys, 10 and 13 years of age, were well developed and healthy in appearance, but on questioning them and their families the following essential points in their histories obtained: Weakness after slight exertion; headaches and tachycardia, particularly the older boy; epistaxis, discomfort and coldness in legs on exertion; marked limitation of activities. Orthopnea was of great concern to the 13 year old and his parents.

These complaints were associated with hypertension in the head, neck, and shoulder girdle with low blood pressure in the rest of the body. No femoral pulse or blood pressure was elicited in either boy's lower extremities. The oscillometer readings were negligible; there was 3 to 7 degrees lower temperature of the skin of the toes to that of the fingers. X-rays of the chest showed notching of the ribs. Angiocardiograms revealed a stenosis at the isthmus of the aorta.

A successful operation was performed on the 10-year-old boy. The 13-year-old boy was operated on three days later. The procedure was more difficult because of his well-developed chest and shoulders and the tremendous collateral circulation in the chest wall.

In the first case the stenosed area was just distal to the junction of the arch of the aorta and subclavian artery at the attachment of the ligamentum arteriosum. The arch was clamped and the subclavian artery temporarily tied with a Penrose drain. The modified Potts' clamp as used by Dr. Blalock would have aided greatly in this case. The distal end of the aorta was clamped with a modified gastrointestinal clamp. The end-to-end anastomosis was completed with 5-0 silk, using a continuous mattress suture. The stenosis in the second case was approximately 2 cm. below the left subclavian artery, which was also stenosed in its first inch as it arose from the aorta and accounted for the 40 mm. of mercury of systolic blood pressure difference in the right arm over that of the left arm. The end-to-end anastomosis was carried out as suggested by Gross. Both boys have made satisfactory recoveries.

I should like to ask Dr. Bing if the eyegrounds were studied, and also what

kidney function tests other than blood flow were made in these cases. We hope to do that in the cases we now have at hand.

DR. NORMAN E. FREEMAN, San Francisco: Dr. Blalock has just presented a fine series of cases and his results have been remarkable. There were two patients in his series, I believe, in whom the aortic lesion was found to be inoperable. I should like to mention a method for visualization of the aorta which may be of help in selection of cases for operation. This technic is quite similar to that so beautifully demonstrated by Dr. Crafoord.

Fariñas of Havana, Cuba, described a procedure for catheterization of the abdominal aorta through the femoral artery. Subsequently, he injected the contrast medium in a retrograde fashion directly into the femoral artery. With sufficient force, visualization of the abdominal aorta and its branches was obtained. Dr. Earl Miller of the Department of Radiology and I became interested in this technic of retrograde arteriography and, in November, 1946, had occasion to use it for visualization of the thoracic aorta. The patient was a woman of 26 with hypertension, who was admitted on the service of Dr. Howard C. Naffziger for surgical treatment. The resident staff noted absent femoral pulsations and, accordingly, the diagnosis of coarctation of the aorta was made. Dr. Naffziger referred the patient to me for operation. There was, however, very little collateral circulation about the upper thorax, no notching of the upper ribs by x-ray and no murmurs over the precordium or paraspinal region between the scapulae. There were dilated collaterals about the lower thorax, umbilicus and flanks and a systolic murmur was audible in the region of T<sup>12</sup> posteriorly and in the epigastrium. Injection of a contrast medium in retrograde fashion into the left common carotid artery demonstrated a normal thoracic aorta. The exact site of the coarctation was not definitely visualized but the x-ray examination proved that the narrowing was not in the usual location. Subsequently, Dr. H. Brodie Stephens, Dr. Mary Olney, Dr. Miller and I, with the help of the house staff, have developed a simple technic for retrograde arteriography, which has now been used in 14 patients in whom the diagnosis of coarctation of the aorta was suspected. The results in this series were reported last month before the American College of Physicians.

Under general or local anesthesia the left common carotid artery is freed up for a distance of 5 cm through an incision above the left sternoclavicular joint. It is surrounded by a segment of rubber tubing. With the patient lying flat on his back, preliminary films are taken and then a needle is inserted into the carotid artery and directed toward the aorta. This needle is connected by a short segment of rubber tubing to a syringe containing 70 per cent diodrast. In children, a No. 18-gauge needle is used and 10 to 20 cc. are injected. In adults we have found that a No. 16 needle is preferable with 50 cc. of solution. With the distal carotid temporarily occluded by rubber tubing, the solution is injected as rapidly as possible and serial x-ray films are taken. After exposure of the films the diodrast remaining in the left carotid is aspirated back into the syringe. By means of this technic we have obtained visualization of the aorta and its branches. The site of the coarctation of the aorta has been established in 11 cases. In three patients it was demonstrated that for various reasons, operative correction was not indicated.

DR. JOHN C. JONES, Los Angeles: We have operated upon 13 patients for coarctation of the aorta and completed some type of anastomosis in all. The end of the subclavian was anastomosed to the side of the distal aorta in two patients. The coarctation was resected and the end of the subclavian was anastomosed to the end of the distal aorta in two instances, and in nine patients the coarctation was resected and an end-to-end anastomosis of the aorta completed. The ages of these patients ranged from two and one half to 31 years. There were 2 deaths in the series. One was a 31-year-old male with a large heart who had been decompensated for two years. He had advanced arteriosclerosis and, after we were able to complete



a satisfactory anastomosis, the posterior wall of the aorta at the site of the proximal clamp developed a leak on removal of the clamp. This was repaired with some difficulty, but he died suddenly on the ninth postoperative day of a dissecting aneurysm, well proximal to the anastomosis, which was intact at autopsy. The other death was a male of 17 years in whom we had no difficulties in resecting and completing an end-to-end anastomosis, but he died suddenly four hours after operation, presumably of a leak or rupture at the site of anastomosis.

The seven survivals of the resection with end-to-end anastomosis of the aorta have had excellent results, with blood pressures in their legs as high as if not higher than in the arms. The two patients in whom the end of the subclavian was anastomosed to the end of the distal aorta likewise have been excellent results. The two patients in whom the end of the subclavian was anastomosed to the side of the distal aorta are improved, but the results might be estimated as only fair.

We have operated upon three patients of 5 years or younger; one was two and one-half years old and his, incidentally, was the easiest operation from a technical point of view. He had the smoothest postoperative course and he was able to go home on the tenth day after operation.

Since the collateral circulation is well developed early in life in these individuals, the indications are to operate upon them early. We have employed a variety of methods in our end-to-end anastomoses of the aorta, but at present prefer the use of four everting stay sutures combined with four running over-and-over sutures in the four quadrants.

DR. H. B. SHUMACKER, JR., New Haven, Conn.: Dr. Crafoord's very interesting discussion of the excellent paper by Dr. Blalock and Dr. Bing prompts me to describe briefly some experimental observations upon arterial suture which my associates and I have recently carried out. We have compared the results of end-to-end arterial suture performed by various suture technics, principally the everting mattress suture which Dr. Blalock has used and the direct anatomic layer-to-layer approximation which Dr. Crafoord has employed. Histologically, one gained the impression that the direct anatomic repair resulted in nicer repair, but functionally there was no doubt that the everting mattress technic was superior. When specimens were removed at varying intervals after suture it was evident that complications such as stricture, dehiscence, and the formation of small aneurysms at the site of suture were much less common when everting mattress sutures had been used. There was no significant difference in the incidence of thrombosis with the two methods. We were led to the conclusion that the everting mattress technic was preferable.

We also tested the breaking strength and the ability to withstand intraluminal pressure at varying intervals after end-to-end arterial suture. The recently sutured vessel will pull apart with little force but rapidly gains in strength, approaching normal values in a few weeks. Such repaired arteries withstand without bursting or leaking intraluminal pressures far in excess of systolic blood pressure even a few hours after repair, and within two weeks they withstand without difficulty pressures as high as or higher than do adjacent normal segments of the same artery.

DR. R. J. BING, Baltimore (closing): Dr. Blalock and I would like to congratulate Dr. Crafoord on his beautiful work. In addition, we would like to thank everyone who has participated in the discussion of our paper.

We are particularly interested in Dr. Crafoord's method of arterial angiocardio-graphy. The method certainly appears to give beautiful pictures of the area of coarctation and seems worth while repeating in this country. The problem brought up by Dr. Fell about kidney function and coarctation has been examined at the Johns Hopkins Hospital by Dr. Genest and his co-workers. These investigators reached the conclusion that in many cases of coarctation the glomerular filtration rate is normal, while the effective renal plasma flow is decreased. These findings would indicate constriction at the side of the efferent arterioles.

# ✓ THE PORTACAVAL SHUNT IN THE SURGICAL TREATMENT OF PORTAL HYPERTENSION

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THE RATIONALE of establishing an anastomotic shunt between the portal and caval systems of veins for the relief of portal hypertension has long been appreciated. In the belief that advances had taken place in surgery which may have a bearing upon the clinical success of portacaval shunts, Dr. Allen Whipple and I undertook a restudy of the problem in 1943.

This paper will be limited essentially to a discussion of the results in a series of 58 cases in which portacaval shunts were established. The operation was performed by either Dr. Whipple or myself in 48 of the series of 58 cases with a loss of 8 cases postoperatively. There were 11 postoperative deaths in the entire series. The cause of death in the eleven cases was as follows: Cholemia = 3 cases; cerebral damage = 2 cases; cardiac failure = 1 case; mesenteric thrombosis = 3 cases; shock from intraperitoneal hemorrhage = 1 case; gastro-intestinal hemorrhage = 1 case.

Space does not permit a critical analysis of each of the eleven postoperative deaths but a short discussion is timely.

In one of the three cases dying of cholemia, necropsy examination revealed liver cell degeneration compatible with an active virus hepatitis. Whereas there were also present periportal fibrosis and esophageal varices (the man had hemorrhaged once); nevertheless it was an error in judgment to have brought him to operation at the time, and, for the following reasons: (1) Recent (3½ mos.) history of virus hepatitis; (2) persistence of anorexia, exhaustion, jaundice and ascites; (3) persistence of a four plus cephalin flocculation test, reversal of the serum albumin-globulin ratio (albumin 1.9%, globulin 4.4%); and an elevated prothrombin time (50% of normal). We operated upon this case early in our experience, but we now know that we should have waited until evidences of active hepatitis had disappeared.

A second case who died of cholemia was that of a 59-year-old man having Laennec's cirrhosis of the liver complicated by tertiary syphilis. This patient in spite of a 9 months' trial of a dietary liver regimen, remained in a state of chronic liver decompensation with wasting ascites. Throughout this period his serum albumin gradually fell from 3% to 2.4%. There was no improvement in bromsulphalein excretion-retention which remained at 40% one-half hour after injection. Over much of the time cephalin flocculation tests were three and four plus, galactose removal constant and prothrombin times were 50% of normal. Though the serum phosphatase was, on most examinations, slightly elevated, the serum bilirubin remained normal. The decision to operate in this case was further influenced by the presence of demonstrable esophageal varices. A splenorenal type of portacaval shunt was established in this case. On the third postoperative day he became comatose and on the fourth day he died.

We now believe that the above described case might have survived the portacaval shunt procedure if for several weeks prior to operation, carbohydrate and protein feedings had been forced to the limit, using if necessary, intravenous albumin to help lessen the ascites and edema. Cyclopropane

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\* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

instead of ether anesthesia would, in our opinion, have given him a better chance. Though admittedly his liver function studies classify him as a poor operative risk, we have two cases who survived portal vein to venacava anastomoses who were strikingly similar. Both cases became ascites free following operation. One of the patients gained 50 lbs. in weight and continues his work as a timber cruiser now 3 years since operation. The other case survived a strangulated hernia operation two months following the portacaval shunt procedure and carried on ascites free for 1½ years. At this point the patient became somewhat stuporous and the tongue became beefy red. One month later, he developed ecchymosis with the appearance of bloody ascites and a prolonged prothrombin time. During the third month of progressive liver failure, the course was rapidly downhill. There was a terminal rise of the blood urea nitrogen to 63 mg. %.

The third postoperative death assumed to be due to cholemia in the series was that of a 47 year old man who first entered the Presbyterian Hospital in 1940 with virus hepatitis. After a two months stay in the hospital the jaundice had cleared and the cephalin flocculation test returned to normal. Four years after the hepatitis the patient had his first attack of gastro-intestinal hemorrhage. In September 1947, the patient was readmitted to the Presbyterian Hospital stating that in January and July of that year, he had had episodes of hematemesis. Examination revealed an enlarged liver and spleen. The blood picture was that of Banti's syndrome. The cephalin flocculation and thymol turbidity tests were each three plus. The serum albumin was 4.3% and globulin 2.5%. Catheterization of the hepatic vein in this case revealed a 50% reduction in hepatic blood flow, with a high oxygen content but a 90% of normal extraction of bromsulphalein. These findings indicated the perfusion of considerable normal liver tissue with a high component of arterial (hepatic artery) blood. Roentgenograms revealed varices practically throughout the length of the esophagus.

The patient was considered a good liver risk for a portacaval shunt. On the 14th of October, 1947, he was operated upon. The liver was enlarged, irregularly nodular and firm. The gallbladder contained stones and the spleen was greatly enlarged. A splenectomy was performed and followed by a splenorenal shunt. Opening the shunt lowered the portal pressure from 370 to 270 mm. of water. A cholecystectomy was also done. The postoperative course of this patient until his death on the 29th day, well illustrates the ultimate seriousness of a cycle of complications in cases with liver damage.

The patient, starting out with the necessity of repeated catheterization and finally continuous catheter drainage because of an old urethral stricture, developed urinary tract infection. A bilateral pneumonitis followed and upon recovering somewhat from this, the patient developed phlebotrombosis of the femoral veins. Heparin therapy was instituted for this. Finally, on about the 16th postoperative day, the patient's temperature went higher accompanied by diarrhea and abdominal distention. This period was punctuated by gastro-intestinal bleeding. We considered strongly the diagnosis of mesenteric thrombosis at this point, but rather suddenly his abdominal distention and diarrhea ceased and his temperature went still higher. Two blood cultures were made at 9-day intervals. Salmonella Montevideo bacilli were recovered from each flask. During the last 10 days of the patient's life, he presented the picture of marked sepsis. The white blood count varied from 50,000 to 70,000 with the polymorphonuclears in excess of 90%. Some five days before death the patient developed a mild jaundice and two days before death, coma supervened.

We assumed that the above patient died of liver failure but it is of

interest that at six and two days before death, the serum albumin was 3.2% and 3% respectively. Unfortunately, no necropsy was obtained in this exceedingly interesting and complicated case.

The two postoperative deaths of the series in which cerebral pathology played a role are worthy of mention.

One a case of cirrhosis of the liver and lenticular degeneration of the brain (Wilson's disease). This 29-year-old man, during a year of observation upon an excellent liver regimen developed increasing signs of cerebral damage with an increased incidence of gastrointestinal bleeding. On the above account on September 10, 1947, a splenectomy and a splenorenal shunt procedure was carried out. Following operation, the temperature rose to 104°F. and was maintained at that level for 3 days. The patient became extremely euphoric and on the fourth postoperative day lapsed into coma. From this point until his death, two days later, his coma was punctuated with attacks of what appeared to be "sham rage".

Whereas slight jaundice did develop in the above case after the onset of coma it seemed unlikely to us that the coma was explained solely on the basis of a failing liver. His serum albumin which was 3.5% five days before operation fell to 3.4% two days after operation but was 3.6% the day before his death. We have not infrequently noted slight jaundice to develop in other cases a few days after operation in which multiple transfusions were employed. It seemed more likely to us that the cerebral pathology played a primary role in the coma in this case. Unfortunately, no necropsy was obtained in this case. At operation the large nodular liver with intervening scarring suggested the appearance of a liver following an attack of subacute yellow atrophy in which the surviving lobules have undergone hypertrophic enlargement. On microscopic examination the liver cells were frequently large and bizarre. The intervening scar tissue and liver capsule were infiltrated with lymphocytes with an occasional eosinophilic leucocyte.

The hepato-lenticular syndrome (Wilson's disease) is poorly understood. The course of the disease is usually rapidly downhill, and from what I can learn, they are inherently poor operative risks.

The second cerebral death in the series was that of a 23-year-old woman who had multiple arteriovenous shunts between the splenic artery and vein. As evidence of portal hypertension, there was a history of repeated hematemesis. At operation following removal of the spleen, the portal pressure fell but did not return to a normal figure. Accordingly, a splenorenal shunt was done because it was thought that some inaccessible arteriovenous shunts remained. The operation was carried out under cyclopropane and with minimal blood loss. The blood pressure was at no time below 100 systolic during the procedure and the patient was well oxygenated during the period. The first indication of a cerebral accident in this case was failure of the patient to wake up promptly and become responsive following cessation of the anesthesia. Although, a few hours later the patient could be aroused and answered questions, there were unmistakable neurologic findings of a cerebral accident. Her condition rapidly became worse and death occurred on the second postoperative day.

A complete autopsy revealed the anterior and middle cerebral arteries on the right to be filled with blood clot with extension of the clot into the right carotid artery. Careful search revealed no source of embolus. There were no septal defects in the heart. The splenorenal anastomosis was free of clot.

The mechanism by which blood clot became deposited in this young woman's cerebral arteries remains unexplained. She was given the usual dose of heparin when the portacaval shunt was opened and had a satisfactory rise in the blood clotting time. The heparin was given some thirty minutes before the anesthetic was stopped and it seems illogical that a thrombosis could take place, after the administration of heparin. If the accident is to be explained on the basis of a thrombosis, it must have occurred earlier in the operation.

Cardiac failure was the cause of death in one case.

A 64-year-old widow entered the Presbyterian Hospital on April 21, 1947, complaining of generalized weakness for 3 months and pain in the left side for 3 weeks. The patient gave no history of hepatitis. She rarely took alcoholic drinks. There was no history of hemorrhage, ascites or jaundice. On examination the blood pressure was 160/80. Roentgenogram showed an enlarged heart with a silhouette suggesting right and left chamber enlargement accompanied by left ventricular hypertrophy. On the other hand, the patient gave a negative cardiac history and the only heart finding on physical examination was a soft systolic blow at the apex. The prominent findings were an enlarged firm liver and a considerably enlarged spleen with a severe anemia of the hypochromic type. The blood platelet and white cell count was markedly reduced.

Examination of the bone marrow was negative except for a slight increase in normoblasts. The prothrombin time was 18 seconds (normal 14 + 1 second).

The liver chemistry was as follows: Serum bilirubin faint trace; cephalin flocculation 3+; serum phosphatase 7.1 Bodansky units; total protein 7.3%; albumin 3.9%; globulin 3.4%. The bromsulphalein liver function test revealed 90% retention 5 minutes after injection and 30% retention after one-half hour.

The electrocardiogram showed left axis deviation with evidence of myocardial damage. The gastro-intestinal series of roentgenograms showed diverticula of the colon. The intravenous pyelogram was negative.

On May 9, 1947, the patient was explored and the findings were as follows: The liver though enlarged was not nodular nor was the capsule thickened. The gall bladder was thick walled and contained calculi. The spleen was firmer than normal and approximately four times normal size.

Portal pressure proved to be 240 mm. of water. On the basis of our figures considered as normal, this represents a rise above normal of 130 mm. of water. Accordingly, a splenorenal shunt was done following removal of the spleen.

The patient did exceedingly well postoperatively for the first two days. The venous pressure ranged from 84 to 90 mm. of water. On the morning of the third postoperative day the temperature was 100.4° F., the blood pressure and pulse were satisfactory but a few coarse rales were heard at the right base and the venous pressure had risen to 127 mm. of water. The patient suddenly died in her sleep in the early morning of her fourth postoperative day, presumably of cardiac failure. No postmortem examination was obtained.

The above case has been presented in detail for the following reasons: (1) Examination of Microscopic sections taken from the spleen and liver showed infiltration of moderately immature cells of the myeloid series, as well as megakaryocytes. In the spleen the cells were found in foci within the germinal centers as well as in the pulp. Sections of the liver reveal foci of similar cells with a tendency to be found with greater regularity in the

portal spaces. The pathologist (Dr. W. Lehman) concludes in the absence of evidence of leukemia in the bone marrow examination and blood smears, that the diagnosis in this case is myeloid megakaryocytic hepatosplenomegaly. (2) Conceding myelofibrosis affecting mainly the portal areas of the liver to be an adequate cause of the portal hypertension and possibly the bromsulphalein retention in this case, the question now arises, should this patient have had only a splenectomy?

Of one thing we are certain. This patient should have been digitalized before coming to operation. It is our present policy to digitalize preoperatively all cases age 50 or over whose electrocardiograms show left sided ventricular preponderance. We now have several cases in their sixties who have gone through portacaval shunt operations successfully.

In the eleven postoperative deaths of the series of 58 cases, there were 3 cases who died of mesenteric thrombosis.

Case 1.—A 39-year-old woman who first entered the Presbyterian Hospital on May 30, 1946, complaining of weakness of five years' duration. On this admission, the patient was found to have a marked splenomegaly, secondary anemia, leucopenia and thrombocytopenia. A bone marrow examination was normal, revealing no cells typical of Gaucher's disease. The cephalin flocculation test was 4 plus. Serum phosphatase 2.5 Bodansky units. Serum bilirubin 1.5 mg. %. Total protein 6.2%. Albumin 3.8%. Globulin 2.4%. Bromsulphalein 90% retention 5 minutes after injection and 25% retention 30 minutes after injection. Serum cholesterol total 159 mg.%, free 36 mg.%, ester 123 mg.%.

A diagnosis of Banti's syndrome was made and the patient discharged for follow-up.

The patient was readmitted to the Presbyterian Hospital on September 7, 1947, unimproved. The liver chemistry studies were essentially the same as on the first admission, except that there had been a rise in the serum bilirubin to 2.2 mg.%. The secondary anemia and thrombocytopenia persisted. There had been no episodes of gastro-intestinal hemorrhage or ascites. Roentgenograms were negative for esophageal varices.

On September 25, 1947, the patient was explored. The liver was found to be the site of a diffuse uniform nodular cirrhosis. The spleen was enlarged about five times normal size. The portal pressure was found to be 400 mm. of water. A splenectomy was done and followed by a splenorenal type of portacaval shunt, end to side by suture. The liver biopsy confirmed the diagnosis of cirrhosis.

The patient ran a temperature to 101°F. daily during 17 days postoperatively. The platelet count gradually rose to normal over this period. Aside from slight ascites which quickly disappeared, there were no other important findings. After a 10-day period of essentially normal temperature, the patient began to have diarrhea and her temperature rose to 102°F. daily. The patient complained of low backache and lower abdominal tenderness. Examination revealed a flat abdomen with no marked tenderness. On pelvic examination on the left side, extending laterally to the left and posterior to the vagina, was a tender sausage-shaped mass. On rectal examination the mass was posterior and to the left of the rectum.

The patient's fever continued. The white blood count rose to 23,000 with 91% polymorphonuclears. A culture of the urine was negative. A stool culture yielded *Salmonella Tennessee*. Her temperature failed to respond to sulfadiazine, penicillin or streptomycin. The abdomen remained essentially soft following the onset of the diarrhea on the 27th postoperative day until the 43rd postoperative day when abdom-

inal distension rather suddenly became extreme. During the last few days of life, the patient became comatose and died on the 45th postoperative day.

The postmortem examination was of extreme interest in this case. The mass noted on pelvic examination on the 30th postoperative day proved to be a thrombosed hemorrhoidal vein. Gram negative rods were present in the thrombus which is of interest in that during the period of diarrhea bacillus, *Salmonella Tennessee* was recovered on stool culture. At necropsy examination the thrombus was found to have extended to include the inferior mesenteric, superior mesenteric and portal veins including of course the splenorenal anastomosis.

Case 2.—The second case of death from mesenteric thrombosis postoperatively is that of a 36-year-old man who was admitted to the Presbyterian Hospital on September 16, 1946. He presented the history of attacks of abdominal cramps followed by bloody diarrhea on two occasions, the first attack 10 years previously. Five months prior to admission there were two episodes of hematemesis. The physical examination finding of note was the presence of an enlarged spleen.

Laboratory studies were as follows: Barium enema roentgen rays were normal. Roentgenogram of the esophagus following a barium swallow showed varices. Stool cultures revealed no enteric pathogenic organisms, no ova or protozoa were found in the stools. Cephalin flocculation tests were 3 plus and one later 1 plus. Serum albumin was 3.9%; globulin 3.1%. Serum phosphatase 2.2 Bodansky units %. The prothrombin time was normal. The galactose tolerance test (intravenous) showed a removal constant of 2, as indicative of liver damage. The blood picture was that of Banti's syndrome, namely secondary anemia, leucopenia and thrombocytopenia.

The patient was explored on November 14, 1946. The liver appeared grossly normal but the spleen was approximately five times normal size. The portal pressure measured 340 mm. of water.

A splenectomy was done, followed by a nephrectomy and an end-to-end anastomosis of the splenic vein with the renal vein by the non-suture vitallium tube method.

Microscopic sections of the spleen revealed the usual picture of congestive splenomegaly. The sections of the liver biopsy revealed areas of slight liver cell degeneration, much pigment but no evidence of specific liver disease.

Following operation, the patient developed pneumonitis complicated by abdominal distension necessitating the passage of a Miller-Abbott tube on the second postoperative day. By the fifth postoperative day the distention of the abdomen had been relieved and the Miller-Abbott tube withdrawn. On the eighth postoperative day the temperature had subsided to normal. The patient had been actively up and about when he suddenly developed abdominal cramps with a return of the abdominal distention. Two days prior to this anticoagulant therapy (heparin) had been stopped. On the eleventh postoperative day abdominal cramps and distention had become markedly worse with the appearance of ascites. The temperature and pulse rate began to rise and on the thirteenth postoperative day the white blood count was found to be 37,000 with 90% polymorphonuclears. The platelet count had risen to 192,000.

A paracentesis was done on the thirteenth postoperative day. 2600 cc. of faintly turbid yellow fluid was removed. Whereas a culture of the fluid was reported negative, no examination of the fluid was made for the presence of red blood cells. Following paracentesis though, the abdomen remained greatly distended, and a



sausage-shaped mass could be felt in the right lower quadrant which was thought to be a distended loop of ileum.

On the fourteenth and fifteenth postoperative days, the patient was obviously worse and vomiting had set in. The white blood count was 39,000 with 92% polymorphonuclear cells. The pulse rate had mounted to 130 per minute and the temperature fell precipitantly to below normal. On the sixteenth postoperative day the abdomen was explored. All of the jejunum except for the proximal 3 feet and all of the ileum except for the distal 4 inches were dark purple with thrombosed vessels in the mesentery throughout the affected area. The insidious onset led the operator to believe that thrombosis of the mesenteric veins preceded that of the arteries. A jejuno-ileostomy was performed following resection of the non-viable bowel. The patient was well supported by transfusions and he stood the operation well.

The patient was given penicillin and streptomycin following the bowel resection and for a few days seemed better. However his temperature began to rise from normal on the third postoperative day and in spite of the presence of a Miller-Abbott tube, dilated loops of bowel was shown by Roengen ray. The patient's blood urea rose progressively and on the sixth post-resection day he became jaundiced. Acidosis developed. After the administration of 400 mil. equivalents of sodium lactate, the patient's  $\text{CO}_2$  rose from 25 to 35 volumes percent and the plasma sodium rose from 110 to 129 M.E. In spite of these attempts to correct the electrolyte imbalance, the patient lapsed into coma, the temperature continued upward to  $104^\circ \text{F}$ . The patient died on the tenth day following intestinal resection and the 26th day following the establishment of a splenorenal shunt.

The important postmortem findings in the above case were as follows: Peritonitis, fibrino-purulent, generalized; abscess, right lower quadrant; dissolution, anastomosis site of ileo-jejunostomy with leakage of intestinal contents into the abscess cavity. The liver in the gross and microscopic examination was free of cirrhosis. The pancreas on section showed thrombosis of the smaller veins. There were areas of fat necrosis in the surrounding mesentery and omentum.

The alimentary tract revealed numerous large varices in the esophagus without evidence of ulceration or recent hemorrhage. The stomach was distended with edema of the mucosa which was dotted with petechial hemorrhages. The duodenum was also distended. The large intestine appeared normal.

The portal venous system was extremely interesting. The lumen of the portal vein had been replaced by interlacing white fibrous trabeculae which form a number of small canals. Under microscopic examination it was noted that these recanalized blood spaces within the portal vein were lined in part by endothelium. In addition two large rather recent thrombi were undergoing early organization with invasion of fibroblasts and capillaries at the site of attachment to the masses of fibrous tissue. Dark red thrombi were seen to extend into the splenic vein and superior mesenteric vein.

The above pathologic findings present the picture of cavernomatous transformation in all stages of recanalization including old organizing thrombus with extension of recent thrombus retrograde, throughout the portal radicals including the splenorenal shunt. What better nidus could there be for the



initiation of a postoperative mesenteric thrombosis! It seems logical that careful attention to the avoidance of postoperative distention and anticoagulant therapy properly administered will offer the best chances of preventing the formation of new thrombus in such cases in the future.

The third case of postoperative death due to mesenteric thrombosis was that of an obese middle aged woman having cirrhosis of the liver.

Following the establishment of a splenorenal shunt the operator decided to administer heparin hypodermically at six-hour intervals for some six or more days postoperatively. Toward the end of this period, the patient's abdomen became progressively more distended, ascites formed, she finally became jaundiced and died in cholemia. Necropsy revealed thrombosis of the portal vein with all of its branches including the splenorenal anastomosis.

In my opinion, pure heparin solution administered hypodermically at such long intervals as six hours apart may even predispose to the development of thrombosis at the site of a recently performed portacaval anastomosis. I base this opinion on recent unpublished observations made by Dr. Arthur Voorhees while working as a surgical fellow. Dr. Voorhees has done many highly accurate blood clotting determinations. He finds that in many people following the administration of a single dose of heparin, when the heparin effect upon the clotting time wears off, for an hour or more thereafter, the blood clotting time goes down to 50 or more per cent below the normal clotting time for that individual. We have found out that the best way to prevent this extremely undesirable effect is to administer heparin either intravenously in normal saline solution by a carefully controlled drip, or hypodermically at two-hour intervals.

The one death from shock due to intraperitoneal hemorrhage was solely the result of technical failure.

The case was that of a 54-year-old Cuban male who for one year had suffered from ascites due to portal cirrhosis of the liver.

Varices of the esophagus were demonstrated by roentgen-ray. The total serum proteins were 5% albumin, 3%, globulin 2%.

On August 15, 1945, the patient was operated upon. The liver was cirrhotic and extremely small. The portal vein was mobilized but upon mobilization of the venacava, the right renal vein was found to join the venacava extremely high. Accordingly the right kidney was removed and an end-to-end anastomosis established between the portal and renal veins employing the non-suture method. The abdomen was closed practically before it was discovered that a massive intraperitoneal hemorrhage had occurred. On reopening the wound it was found that the hemorrhage had resulted from a torn omental vein which for a considerable period had gone unobserved. The shock from this additional loss of blood was calamitous for the patient and he failed to revive in spite of the quick administration of a large amount of blood and plasma.

The above death from hemorrhage due to faulty hemostasis occurred early in our experience. The case taught us much about operating in the presence of severe portal hypertension.

I report the eleventh postoperative death as representing a series of tragedies.

The case was that of a 47-year-old housewife who entered the Presbyterian Hospital with the complaint of three attacks of vomiting of blood during the two years prior to admission and swelling of the abdomen of three months duration.

The patient gave a negative history of exposure to hepatotoxins. Starting in 1935, the patient had an attack of nausea with loose bowel movements. There was no associated abdominal pain, fever, jaundice or vomiting. The identical attack recurred in 1941. Between August and October of that year, the patient had 9 attacks. In none of them was there any abdominal pain or jaundice. A cholecystogram revealed the presence of gall stones and in October, 1941, the gall bladder was removed. For a 9-day period following operation, the patient was jaundiced. From 1941 until the time of her first hematemesis (July, 1946) the patient had been free of symptoms. During the attack of hematemesis much blood was lost but there were no other prominent symptoms. Three attacks of massive gastro-intestinal hemorrhage occurred over the ensuing two years. Ascites and edema of the lower extremities appeared following an attack of bleeding 3 months prior to admission.

Physical examination revealed a pale, somewhat obese woman who presented the following pertinent findings; namely, a very large spleen, a large firm liver, and some ascites and pitting edema over the sacrum.

The laboratory findings were as follows: Serum bilirubin negative; serum phosphatase 4.4 Bodansky units %; non-protein nitrogen 17 mg.%; total serum proteins 6.5%; albumin 3.9%; globulin 2.6%; cephalin flocculation 3 plus; thymol turbidity 3 plus. Bromsulphalein 50% retention 5 minutes after injection and 25% 30 minutes after injection. Prothrombin time 17.3 seconds (normal 14 plus or minus 1 second). A gastro-intestinal series of roentgenograms revealed the presence of esophageal varices. The intravenous pyelogram was negative. The red blood count was 3,240,000 hgb. 9. Gm.; WBC 6,450. Platelets 106,000; reticulocytes 2%. Blood clotting time 20 minutes (Lee White method).

At operation the patient got a bad start, having a persistent nosebleed following the introduction of the intratracheal tube. When the skin incision was made, hemorrhage from minute vessels warned us of a bloody procedure. In view of this fact it was thought wise to set up for an arterial transfusion. Accordingly, a cannula was introduced into the right radial artery at the wrist and a transfusion started. The spleen was removed through a left thoraco-abdominal approach. The spleen was adherent to the diaphragm and some six times normal size. The liver was large, firm and nodular on the surface. The patient's extreme tendency to bleed made the problem of hemostasis terrific and greatly complicated and prolonged the procedure.

Finally, after removing the spleen and mobilizing the splenic vein stump, we exposed the left kidney and encountered another difficulty; namely, subcapsular hemorrhage. The kidney was completely mobilized, brought forward and compressed by a gauze pad. An end-to-side splenorenal anastomosis was performed by suture technique, but upon returning the kidney to its bed it was noted that subcapsular hemorrhage had spread to the point of necessitating a nephrectomy. The stump of the renal vein distal to the anastomosis site was repaired following nephrectomy. The patient left the table in remarkably good condition having received 5000 cc. of blood via arterial transfusion. The case was a supreme test for this method of administering blood and the blood pressure was maintained magnificently throughout the procedure.

At this point, I want to call attention to a serious complication of arterial transfusion that was evident in this case at the conclusion of the operation; namely, ischemia of the fingers of the hand. As the result of the use of a glass cannula in the right radial artery at the wrist, it was necessary to

ligate the radial artery at this level. In this particular case there was congenital absence of inosculating branches between the ulnar and radial arteries, and gangrene of the second, third and fourth fingers and tip of the thumb resulted. The necessity for ligation of the radial artery in this case could have been prevented by the use of a baby Lindeman needle.

Aside from the above mentioned complication, the patient's condition was satisfactory for the first 24 hours after operation. It was noted on the second day, however, that her respiration and pulse rate rose sharply. The latter were labored with marked laryngeal stridor. Laryngoscopy and bronchoscopy revealed blood clot between the vocal chords and a large plug completely obstructing the left bronchus. Removal of these obstructions gave temporary relief but atelectasis of the left lung recurred, the patient again became cyanotic and laryngeal stridor returned. The rapid heart rate and rising temperature were ominous. Tracheotomy was done following which another large plug was removed from the left bronchus. Whereas the left lung became aerated, the temperature remained high as well as the respiratory rate. On the fifth postoperative day, the patient's white blood count was 24,000; hgb. 8 Gm.; RBC 3,200,000. The blood pressure had dropped precipitantly from 130 systolic to 100 and the pulse rate had risen to 140 per minute. Hemorrhage was suspected and transfusions started. The patient's blood pressure was boosted for a time with three transfusions but finally, on the sixth postoperative day, she again went into shock and died.

Necropsy examination confirmed the clinical impression of hemorrhage in this case. The stomach and intestines were filled with blood. No exact site of bleeding from the esophageal varices could be determined. The splenic vein up nearly to the site of the splenorenal shunt was the seat of a recent (24-hour) thrombus. The actual anastomosis was noted to be free of thrombus. There was some fat necrosis of the tissues surrounding the pancreas suggesting trauma to the tail of the pancreas at operation. The liver was dotted with nodules and on microscopic examination showed the picture typical of Laennec's cirrhosis.

Many complications might have been avoided in this case if before operation she had been properly prepared with transfusions. The last pre-operative blood count done the day before operation showed 3,160,000 red blood cells and 9.3 Gm. of hemoglobin. In my opinion, the great tendency to bleed in this case was more on the basis of her anemia than of thrombocytopenia. It is now our policy not to operate on cases with severe Banti's syndrome until the hemoglobin has been brought up to 14 Gm. and the RBC to 4,000,000.

We accept this case as one of technical failure, though the actual anastomosis site was not thrombosed.

The eleven postoperative deaths in the series of 58 cases of portacaval shunts have been presented in some detail to illustrate some of the many factors involved in the successful handling of this type of case.

Upon reviewing the cases, one or more serious errors are noted in eight of the eleven cases as follows: Of the cholemic group, the case with active hepatitis obviously should not have been operated upon. Another case was

poorly prepared for operation and should have received cyclopropane anesthesia. It was perhaps an error in judgment to have operated at all on the case of cirrhosis with lenticular degeneration (Wilson's disease). Failure to digitalize preoperatively the case who died of cardiac failure was certainly a serious omission. Two of the three deaths from mesenteric thrombosis involved factors beyond the operators' control but in the third case, in my opinion, an error in judgment in the way heparin was administered postoperatively may have been a contributing factor to the initiation of thrombus formation. In the two cases of death from shock secondary to hemorrhage, certainly errors in judgment and technical failure were directly responsible. I refer to the case dying of massive gastro-intestinal hemorrhage and the case dying of intraperitoneal hemorrhage.

The obligations of surgeons who would undertake a series of portacaval shunts are twofold: (1) To accomplish the operation with a reasonable expectancy of survival of the patient. (2) To employ a surgical technic and routine of postoperative handling that will insure a high percentage of maintained patency of the portacaval anastomoses.

The follow-up histories in our series are dotted with what must be accepted as failures in the sense of the total prevention of the recurrence of hemorrhage.

Of 35 cases who gave a history of severe attacks of gastro-intestinal bleeding before the establishment of portacaval shunts, 11 have had one or more attacks of hemorrhage following discharge from the hospital. The follow-up time ranges from a few months to three or more years.

Analysis of these 11 cases reveals that five of the cases had previously had splenectomies. Four of the five cases had extrahepatic portal block making it unfeasible, as we have routinely found by experience, to employ the portal vein in establishing a portacaval shunt. The types of portacaval shunts established in these four postsplenectomy bleeders were as follows: stump of splenic vein, end to side, with the venacava equals one case; proximal end of inferior mesenteric vein with the venacava, end to side equals one case; superior mesenteric vein to venacava, side to side, equals one case; superior mesenteric vein, distal end to side of the venacava, equals one case.

In the one post splenectomy bleeder in which the cause of the portal hypertension was due to cirrhosis of the liver, the distal end of the portal vein was bridged to the venacava, end to side, employing a vein graft-lined Vitallium tube.

In patients with extrahepatic portal block who have had their spleens removed at previous operations the surgeon is usually limited, as in the above cases, to the choice of employing either the proximal stump of the inferior mesenteric vein or the superior mesenteric vein. The former vein is often so small that even if the anastomosis remains patent, the shunt does

not handle enough blood to furnish absolute protection against the recurrence of attacks of hemorrhage.

Because of the many branches and other anatomic disadvantages it is exceedingly difficult technically to accomplish a side to side anastomosis of the superior mesenteric vein with the venacava. In my opinion it was an error in judgment on the part of the surgeon to have anastomosed the distal end of the superior mesenteric vein to the venacava as previously cited. It is not reasonable to assume that there are sufficient anastomotic branches below the point of section of the superior mesenteric vein connecting with branches proximal to the point of section appreciably to lower the pressure in the coronary vein. Branches of the latter vein inosculate with branches of the esophageal vein and it is the pressure in this vein with which we are primarily concerned in the prevention of hemorrhage from esophageal varices. In this connection it is interesting that the case in which an end-to-side anastomosis of the superior mesenteric vein to the venacava was employed, an attack of hematemesis promptly followed discharge of the patient from the hospital.

Further analysis of the eleven cases whose follow-up history has been complicated by the recurrence of gastro-intestinal hemorrhage is of interest. The splenorenal anastomosis was destroyed by the development of a low-grade infection in one case—the subdiaphragmatic collection of pus on the left was drained some months later. One case was readmitted to the hospital with gastro-intestinal bleeding shortly (2 months) after the establishment of a splenorenal shunt by suture. The patient was in extremis upon her second admission and failed to respond to blood transfusions. Necropsy revealed evidence of bleeding throughout the gastro-intestinal tract. The splenorenal anastomosis was patent. The liver was enlarged and nodular. The common duct was completely filled with small calcium bilirubinate stones. Microscopic sections of the liver revealed the presence of extensive biliary and portal cirrhosis, esophageal varices were present. The true cause of this patient's unremitting, painless, jaundice of some five years duration was not established before or at the time of the splenorenal anastomosis and, to make matters worse, she received no hykinone injections following discharge from the hospital. One can only say in retrospect, that if the common duct obstruction had been relieved first, the patient might now be alive. There is little doubt that portal hypertension was a contributory factor in this patient's attacks of hematemesis over the years prior to admission to the hospital, the portal pressure readings were found to be high. The case stresses the importance of first carefully ruling out obstructive (surgical) jaundice and the necessity of Vitamin K administration in such cases.

The nonsuture method, employing vitallium tubes, was used in six of the 11 cases. The anastomoses have been proved to be closed in two. In five cases the suture technic was employed and in one, a two-year-old child, the anastomosis is proven closed. The above trend in favor of suture anastomosis

fortunately occurred early in our series. As a result, in the large majority of the series of 58 cases operated upon the suture method has been employed.

Early in our experience we became fully cognizant of the many pitfalls in this procedure of establishing portacaval shunts both as to survival of the patient and the successful maintenance of patency of the shunts. For the above reason we have been exceedingly careful in dictating our operative notes in regards to the condition of the veins anastomosed, errors in blood vessel technic etc.,—factors that could possibly influence the continued patency of the anastomoses. In the 11 cases that have given a follow-up history of bleeding it is not surprising, therefore, to find, upon reviewing the operative notes, how frequently technical errors of omission or commission were made. For example, in one case who has had one episode of bleeding during the year following operation, I find in the operative notes that there was a palpable thrill upon opening the anastomosis due to slight twisting of the splenic vein. Though attempts were made to fix and hold the vein in an untwisted position by the placement of fine silk sutures, nevertheless the thrill did not entirely disappear.

Assuming that one could routinely accomplish the perfect suture anastomosis, there yet remain factors which can influence the outcome in regards to sustained patency of the anastomoses. Granted that one can prevent or control postoperative distension or, with anticoagulant therapy, control blood clotting over the three or four day period of endothelialization of the suture line, there yet remains the factor of the normality of the veins anastomosed. The latter we consider one important factor that should influence the operator's decision as to the type of portacaval shunt to employ.

In our series of 58 cases there were 16 cases in which the portal hypertension was secondary to extrahepatic, portal block. In such cases our experience so far, because of the high incidence of involvement of the portal vein, has led us to depend primarily upon the splenic vein for the establishment of a portacaval shunt.

In 42 of the 58 cases the cause of the portal hypertension was intrahepatic. In such cases the portal vein to venacava type of portacaval shunt can usually be employed. As to the question of which type of portacaval shunt:—the splenic vein to renal vein, or the portal vein to venacava anastomosis, has the highest likelihood of remaining permanently open, in my opinion the odds favor the latter. In the first place the portal vein, due to its thicker wall, will withstand years of portal hypertension without undergoing any appreciable degenerative changes that may effect the success of an anastomosis. Such is not the case with the inherently thin-walled splenic vein. The latter is often found to be greatly dilated with sacculated areas in which the wall is thinned out. Areas of sclerosis with intimal plaques are encountered and, in some instances, areas of reduplication of the intima.

In the splenic vein many pancreatic branches are encountered which, when ligated and cut, become promptly filled with clot. This clot in itself contributes a nidus, which, under certain postoperative conditions, may serve to initiate thrombus formation. The portal vein, however, near the site for the anastomosis, is essentially free of tributaries. In an end-to-side anastomosis with the venacava, for example, usually one, and never more than two tributary ligations are necessary. And, in case a side-to-side anastomosis is done, with the use of a special clamp, it is possible to complete the operation without ligating a tributary of the portal vein.

Last but not least in importance, is the anatomic setting in relation to the choice between the splenorenal and the portal to venacava types of portacaval shunt. In the first place, unlike thick-walled arteries, which carry blood under high pressure, the portal radicals are thin walled and are subjected to changes in intra-abdominal pressure following the establishment of portacaval shunts far in excess of the intravascular pressure. For the same reasons, the portal vein is thicker than the splenic vein and its anatomic relations are not such as to make it as subject to compression by contiguous organs or tissues as occurs upon completion of the splenorenal shunt. The tail of the pancreas, for example, will so frequently flop over and obscure the anastomosis upon repositioning the kidney at the very time one is most interested in getting a final glance at the splenic vein and the anastomosis. The colon, in turn, is nearby, ready, with the slightest over-distension, to compress the tail of the pancreas against the anastomosed splenic vein lying directly beneath it. If one resects the tail of the pancreas, the mass sutures required to effect hemostasis inevitably leaves behind more devitalized tissue which, in turn, results in the formation of scar tissue adjacent to the splenic vein. Late contraction of this scar tissue introduces the hazard of constricting the splenic vein.

Finally, in the end-to-side anastomosis of the splenic vein to the renal vein, one is somewhat concerned by secondary contracture of scar tissue about the splenic vein in its retroperitoneal course to reach the renal vein.

How frequently fat necrosis occurs following trauma to or resection of the tail of the pancreas, I am not prepared to state. The pathologist reported the finding in one postoperative death—the case who died of gastro-intestinal hemorrhage.

By comparison, the portal to venacava type of portacaval shunt is singularly free from most of the aforementioned hazards. Though appreciating long ago the likelihood that the portal to venacava anastomosis has the best chance for permanent patency, we have proceeded with caution in its use.

In the series of 58 cases we have employed the venacava to portal vein anastomosis nine times, with one postoperative death. We now have a follow-up of three years in three cases and nearly three years in a fourth. In these long follow-ups on these four cases we have noted no essential differences in the behavior of their cirrhotic livers, either clinically or chemically, from

that of comparative cases upon whom we have employed the splenorenal shunt. One of the cases developed diabetes and attacks of dizziness some two years following operation. The dizzy attacks have occasionally been accompanied by momentary loss of consciousness. Thorough neurologic examinations have failed to explain the attacks except that there is evidence of cerebral arteriosclerosis.

If one plans to do a portal vein to venacava type of portacaval shunt, a thoracic approach through the right diaphragm has certain advantages. For some two years this approach for complicated surgical problems of the liver

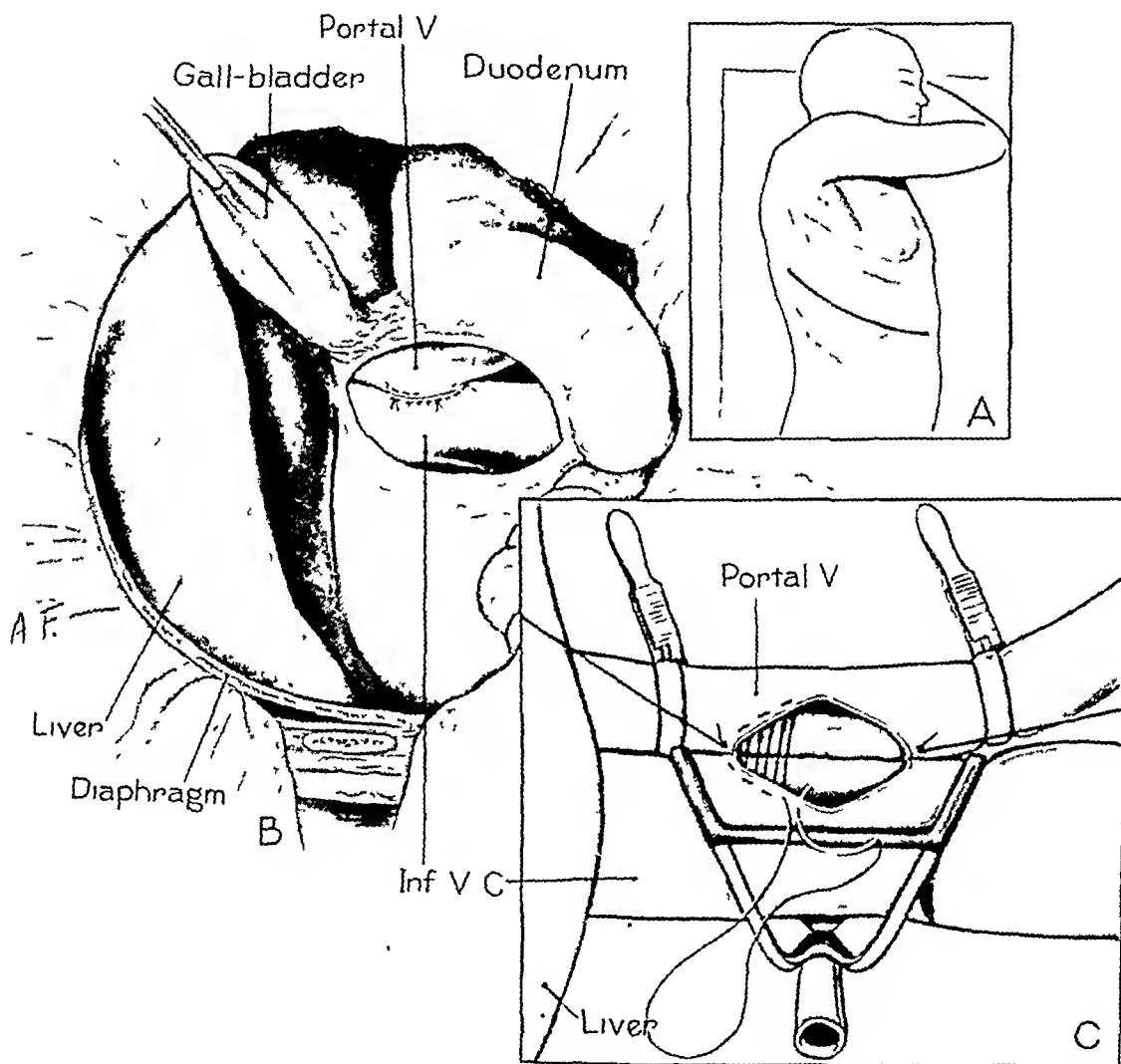


FIG. 1 (A)—Shows the position of the patient on the operating table with the right side up. Note the incision over the ninth rib starts slightly beyond the posterior axillary line and continues obliquely downward and forward to cross the right rectus muscle to the midline of the abdomen. (B.) Illustrates a distinctly lateral approach to the hepato-duodenal ligament. The completed side-to-side anastomosis of the portal vein to the venacava is finally covered by suturing the cut edges of the peritoneum with a few interrupted sutures of fine black silk. (C.) Shows rubber covered clamps in place with the portal vein and venacava being anastomosed. The posterior half of the anastomosis has been completed employing a running everting mattress suture of #00000 braided silk. The posterior running suture is interrupted by tying to three stay sutures, two of which are illustrated. Note, that the transverse incision across the portal vein should extend two or three millimeters beyond the middle. This affords an anastomosis, which when completed, is slightly larger than the cross section area of the portal vein.



and bile ducts has been employed in our clinic with considerable satisfaction by Drs. Humphries and Heeney.

The primary advantage of the thoracoabdominal approach, with the patient lying on the left side, is a distinctly lateral approach to the hepato-duodenal ligament. With this side approach, the peritoneum can be incised directly over the portal vein and the latter dissected free without isolating the common duct (see Fig. 1). The peritoneal incision may be extended to curve laterally around the duodenum for a short distance to permit slight medial mobilization of the latter. The venacava is approached through an incision of the peritoneum directly over it anteriorly. Viewed from the lateral position after incision of the peritoneum, one is impressed with how much the venacava bulges forward—sufficiently, in fact, to touch the portal vein which, when it is freed, bulges backward somewhat to meet the venacava.

After employing the thoracoabdominal approach for the end to side anastomosis of the portal vein with the venacava and observing that the two vessels, after mobilization, touched one another, I have recently done one case anastomosing the portal vein side-to-side with the venacava. The designing of clamps that now permit one to do side-to-side suture anastomoses of the portal vein to the venacava on humans without the necessity of closing off entirely the flow of blood through the venacava, at long last makes the true Eck fistula procedure clinically practical. Figure 1 illustrates the completed side to side anastomosis of the portal vein with the venacava (see legend). Note that due to the fact that the portal vein does not run quite parallel to the venacava the incision has been made transversely in the portal vein for slightly more than half its diameter, whereas the incision in the venacava is more obliquely placed.

It is of interest that opening of the portacaval shunt in this case resulted in a drop in portal pressure to 330 m.m. of water from a previous level of 590 m.m. of water. This large drop in portal pressure represents an additional advantage of the larger portal vein to venacava shunt over the usually smaller splenorenal type of portacaval shunt.

The side-to-side portal vein to venacava anastomosis would seem to offer two possible theoretical advantages over the end-to-side variety, namely: (1) It permits portal blood flow through the liver should ever the pressure relations become conducive to flow; (2) A lessened tendency to thrombosis of the portal vein towards and into the liver. Fear of this more than any other single factor deterred us from using the end to side portal vein to venacava type of portacaval shunt more frequently. This fear was not unfounded, because the one postoperative death in the eight cases in which end to side anastomosis was done did have thrombus extension from the ligated portal vein. However, careful study of this thrombus suggested that it occurred while the patient was in extremis a few hours before death. This was the case of cirrhosis of the liver previously reported as dying of

liver failure secondary to virus hepatitis of recent origin in which evidence of active liver cell damage was still prevalent throughout the liver.

#### SUMMARY

In a series of 58 cases of portacaval shunt, eleven postoperative deaths are reported and discussed in some detail.

There were eleven cases in the series who have had one or more attacks of gastrointestinal bleeding following discharge from the hospital.

In 16 of the 58 cases the portal hypertension was considered to be secondary to obstruction in the portal bed outside of the liver. In 42 of the cases the cause of the portal hypertension was intrahepatic.

The different types of portacaval shunts are discussed and a technic is presented for doing side to side (Eck fistula) anastomosis of the portal vein with the venacava.

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DR. ALLEN O. WHIPPLE, New York: I cannot help but comment on several points. This is a veno-venous anastomosis and is quite a different problem in technic and repair from an arterial anastomosis or an arteriovenous anastomosis. The second point is that the blood pressure, fortunately or unfortunately, drops rather rapidly after anastomosis, which prevents high pressure flow to low over the suture line as one sees it in arteriovenous anastomosis. The third point is the observation made in one case which showed amazing regeneration of the liver following the shunt procedure. This young man was an alcoholic. He developed severe hemorrhage and a diagnosis of cirrhosis had been made before he came to us. It was a question whether he should be operated on. He had a high bromsulfathien retention and a 4+ Hangar test. We attempted the shunt and it was successful. Three or four months later he had an upper abdominal episode and was taken to St. Luke's Hospital and operated on for a perforated duodenal ulcer, and Dr. Adey made some interesting observations on the liver. At the time we operated he had had a marked cirrhotic liver. Dr. Adey found that he had large and small areas of regenerated liver tissue, such as is seen following subacute yellow atrophy. A month or two after that, while convalescing, he went down to Georgia, contracted a hepatitis with mild jaundice and yet survived that.

DR. DUDLEY ROSS, Montreal: I would like to commend Dr. Blakemore's figures on portocaval shunts, but was a little disappointed in his remarks with reference to the splenorenal shunt. At the Children's Memorial Hospital in Montreal we have been particularly interested in knowing whether splenorenal shunts were functioning or not, and for that reason I would like to present to you a suggested procedure for determining the patency of splenorenal shunts.

(slides) This slide shows a catheter introduced into the right median basilic vein, passed down the superior vena cava through the right side of the heart down to the inferior vena cava lying in the left renal vein. This is a patient who had been operated on one month previously for Banti's syndrome. The spleen, which was four or five times normal size, was removed. The pressure of the portal system at operation was found to be 250 mm. of water and the flow from the severed splenic vein appeared to be under pressure that was excessive. Careful search of the splenic vein was made for obstruction at the same time, but none found. The

anastomosis, end-to-side, was carried out and one month later the following test was done. Fasting sugar determinations were made from venous blood at various sites. As you see by the slide, the hepatic vein was 85.5 mg. per cent; the left renal vein was 69 mg. per cent; the inferior vena cava below the junction of the left renal vein was 72 mg. per cent. Then 100 mg. of glucose were introduced by means of the jejunal tube you saw in place in the previous slide, and ten minutes later further readings were taken from the left renal vein, which was found to be 166 mg. per cent and peripheral venous blood 150 mg. per cent. The catheter was left in situ. Ten minutes later another specimen showed 170 mg., in the left renal vein, 158 in the vena cava, and 164 in the peripheral venous blood.

There is no great difference in the fasting state between the vena cava and renal sugar levels, though the renal level is slightly lower. The hepatic vein blood sugar was considerably higher, presumably due to release of sugar from the liver. Following absorption of glucose from the duodenum we find a consistently higher sugar content in the left renal vein than in the vena cava or peripheral vein. We feel that this signifies the functioning of the anastomosis. It is impossible to tell, of course, how much of the portal load is being carried by the shunt, since the portal blood sugar level is not known. The figures, as I have said, indicate that in all probability the shunt is functioning. This child had visible varices. We saw these varices by x-ray before operation, and they had subsided to a considerable extent, so far as x-ray showed.

This work was carried out by Drs. C. A. Allard, Eleanor Harpur and A. L. Johnson.

DR. ARTHUR H. BLAKEMORE, New York (closing): I want to thank Dr. Whipple and Dr. Ross for their discussions. I do not want to give the impression that we felt too blue about the splenorenal shunt. We sincerely feel that in many cases the shunts are still open. We have, by clinical comparison, a good deal of evidence that points that way. I am glad to see Dr. Ross's efforts, which look very encouraging, to determine whether or not the shunts are open. That is certainly very welcome. We are now undertaking some work in the same direction, passing a catheter down the vena cava and a tube in the intestine, in which we plan to put some radioactive iodine in the tube and pick up specimens of blood at different levels from the vena cava.

## CLOSURE OF DEFECTS IN CARDIAC SEPTA\*

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THE HIGH INCIDENCE of defects in cardiac septa in 350 congenital hearts examined, about 50% being diagnosed as patent interventricular or interauricular septa, stimulated my interest in the subject.

Only those defects in the septum which appear to be single lesions are included in this consideration. The perforated septum in tetralogy of Fallot, tricuspid atresia or patent ductus arteriosus and so on are not included and only those are considered when the septum is thought to be the predominant congenital defect and the one causing symptoms.

It is obvious that a small interventricular or interauricular septal defect, in the absence of infection, is of little or no significance. Cases are recorded where soldiers have gone through commando training and through the recent war with known congenital interventricular septal defects with no change in size of heart and no ill effects.

On the other hand, if the septal defect in either auricle or ventricle is large, it is possible that it may be the source of symptoms, and may be accompanied by cyanosis. The symptoms and the cyanosis may depend on several factors, but perhaps the size of the opening is one of the most important, which opinion is supported by Toussig<sup>1</sup> in her recent excellent book on Congenital Heart Disease.

The cases to be considered for operation in my view are those in which the heart is not excessively enlarged; the septal defect is not too large, such as occurs with a single ventricle, and before the patient has reached maturity. On the other hand, they may not be suitable for operation when there is evidence of an enormously enlarged heart with failure, and perhaps a single ventricle instead of a medium sized defect in the septum. I found on post mortem examination of congenital hearts, when a patient has survived to the age of medium childhood or the early twenties, has some cyanosis, has a moderate amount of energy, but with a moderately enlarged heart, that there has been an opening in the interventricular septum of perhaps one to two or more centimeters, in diameter.

In the few cases I have operated on, I was impressed with the high pressure in the pulmonary artery. This on measurement with a monometer was about equal to that of the pressure in the aorta. Whether that high pressure is the result of the septal defect or whether it is accounted for by some congenital anomaly in the pulmonary vascular tree, I do not know. Neither do I know whether this high pressure is reversible if the hiatus in the septum is closed. However, it seemed worth while to attempt to close the hiatus, presupposing that this might be the source of the high pulmonary artery pressure. I have a suspicion that there is some abnormal physiology

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\* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

in the pulmonary vascular tree which may not be remedied by closure of the septal defect alone. For this reason, the problem did not lend itself well to animal experimentation because the septal defects produced artificially in animals were not accompanied by long standing pulmonary hypertension.

Animal experimentation, however, did give us practice in operating on the heart. We learned how much the heart could be manipulated and displaced from its usual position, and its response to stimuli and to transfixion with foreign bodies. With practice, we were able to locate the position of the septum, from the surface markings on the anterior and posterior surfaces of the heart. Using this information we were able to pass needles and probes through the heart anteroposteriorly in the plane of the septum, and place ligatures, crossing artificially formed defects, in the interventricular and interauricular septa. We could see danger signs and learned to judge their significance, and how to relax and rest the heart so that its abnormal responses to stimuli were soon overcome and the circulation was maintained. We were able to proceed with what appeared to be relative safety.

Then came the problem of applying this principle to congenital septal defects in human hearts.

The problem resolved itself into:

- (1) A consideration of the different reactions which might occur in the human heart when compared with an animal heart.
- (2) Secondly, and probably most important, was an anatomic consideration of the area involved, to know what to do, what not to do.

My objective in the interventricular defect was to pass a suture, of considerable size on cross section, through the heart from front to back so that it would pass across the defect in the septum. It was hoped that by slight compression of the heart from before backwards, by this suture, the hiatus could be diminished somewhat in size. Secondly that the substance of the fairly massive living suture would in itself obstruct the hiatus to a degree. If one suture could be passed, then perhaps two or more could be passed in such a way as to interweave them and give fairly complete occlusion of the hiatus. This, accompanied by some local thrombosis, and healing of this area might, with good luck, cause sufficient obstruction of the hiatus to improve the function of the heart and relieve the patient of symptoms.

#### ANATOMIC CONSIDERATIONS

(1) The decending branches of both the right and left coronary arteries are described as passing down in the interventricular sulci anteriorly and posteriorly. These sulci are described in anatomy books as roughly outlining the anterior and posterior margins of the septum. Also, the transverse branches of both left and right coronaries run transversely in the auriculo-ventricular sulcus and these again, are in the field of operation. It was necessary then to go carefully into the anatomy of the heart to know more accurately what are the exact surface markings, of the anterior and

posterior margins of the septum, and so to know at what point in relation to the sulci and coronary arteries the septum can be approached with safety.

(2) The next anatomic structures in direct relationship to the operative field are the valves of the pulmonary artery and aorta anteriorly, and the tricuspid and mitral valves with their chordae tendineae more posteriorly. At the operation, it is necessary to pass the instrument and suture material down between these right and left series of valves so that none of them will be interfered with; so that the cusps are not caught in the suture material; so that the chordae tendineae and the papillary muscles are not caught in the sutures. Any serious interference with these structures would precipitate an immediate disastrous effect.

(3) The next structure to be avoided is the bundle of Hiss, or the conducting bundle which traverses the interventricular septum to reach the papillary muscles and ventricular walls.

These anatomic points will now be discussed in further detail.

The left coronary artery coming from the left sinus of Valsalva, courses toward the heart over a distance of about five-eighths to three-quarters of an inch. Reaching the anterior surface it divides into descending and transverse branches. The right arises from the right anterior sinus of Valsalva, courses distally to reach the posterior aspect of the heart, dividing into the right descending and transverse branches. In the books on the subject, these descending branches are placed in the anterior and posterior interventricular sulci.

To get more accurate information, Professor Grant and Dr. Mahanti dissected 15 hearts to determine the exact relationship of the septum to these surface markings. From within the heart, sutures were passed from both right and left surfaces of the septum, through the heart muscle, reaching the surface on both the anterior and posterior aspects. These sutures in a sense "staked-out" the margins of the septum as they reached the surface on both anterior and posterior surfaces and demonstrated the relationship of the attachment of the septum, to the anterior and posterior sulci, as well as to the descending branches of the coronary artery.

On the posterior surface, the interventricular sulcus corresponded to the attachment of the septum in six. The septum was attached to the left of the sulcus in nine and to the right in only one.

The descending vessels, both arteries and veins, were examined in relation to the septum. The septum was found to be attached to the left of the vessels in eight, over the line of the vessels in five and to the right of the vessels in two.

On the anterior surface, the descending branch appeared to lie more closely in relation to the sulcus than it did in the posterior, and the relationship to the septum was slightly more constant. It was demonstrated that if a point was taken to the right of the descending branch in front, and imme-

diately distal to the auriculo-ventricular sulcus, this fairly accurately marked out the attachment of the septum anteriorly. (Fig. 1)

If with an opaque medium, a defect in the interventricular septum should be demonstrated at a more distal point, such as occurs in the Rogere type, then suitable points in this corridor, both anteriorly and posteriorly would give a direct approach to the site of the defect.

Regarding the valve rings in the annulus fibrosis or skeleton of the heart, there are many diagrams in Quain's, Gray's, Cunningham's, Grant's

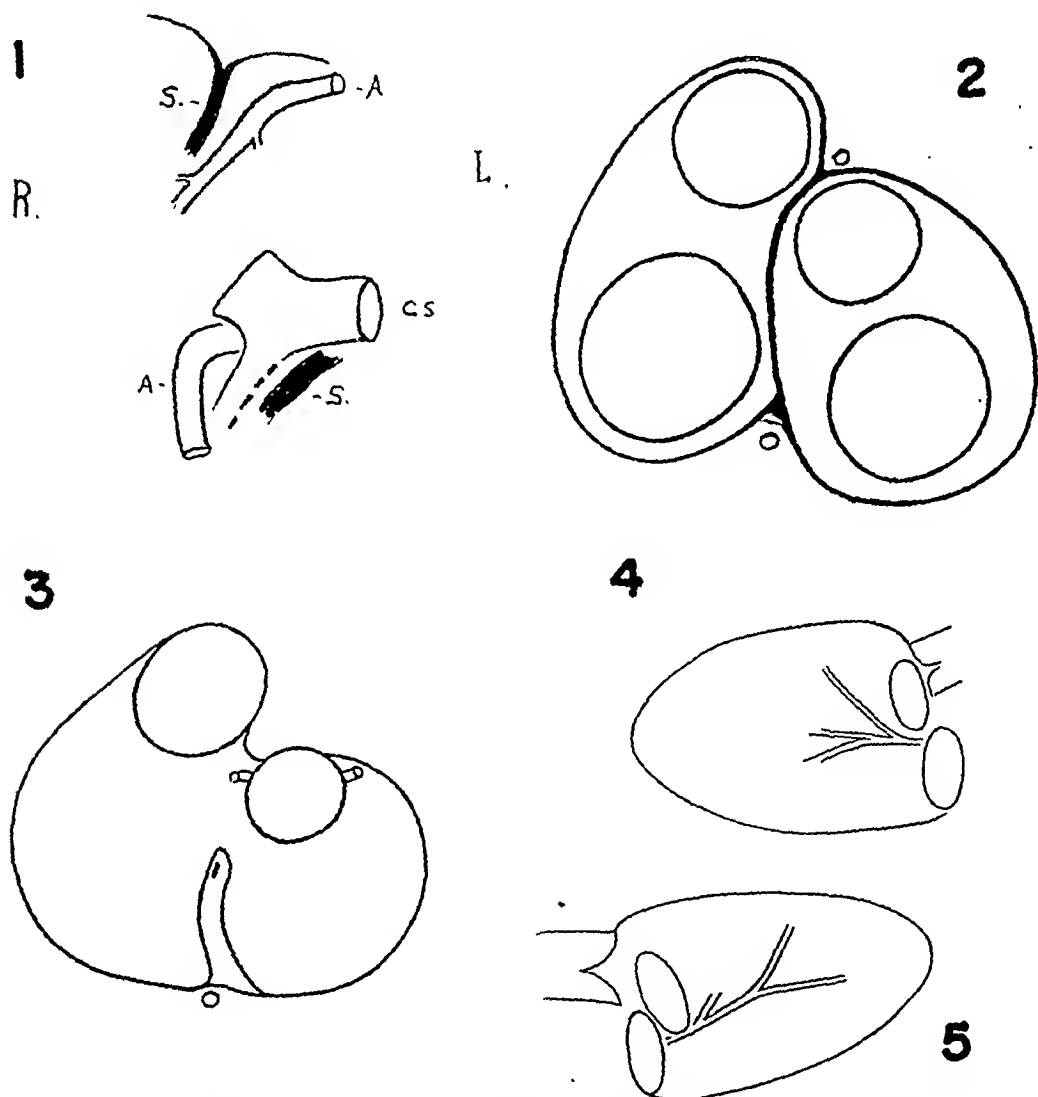


FIG. 1. *Top* S—septum, upper end seen from front and, A—coronary artery anterior descending branch. Showing relationship of upper end of septum to artery.

*Bottom* S—septum A—descending branch right coronary, C S—coronary sinus. Showing relationship of septum to these structures on posterior surface of ventricles.

FIG. 2.—Diagram of annulus fibrosis with ventricles removed, showing valve seats and the relationship of the attachment of the base of the interventricular septum between the right and left groups.

FIG. 3.—Diagram of annulus fibrosis and the attachment of the base of interventricular septum in the presence of a patent septum.

FIG. 4.—Course of Bundle of Hiss seen from left ventricle.

FIG. 5.—Same—seen from right ventricle.

Atlas, Buchanan's and in many of the anatomies. To get further details, we did many dissections, again with the assistance of Professor Grant, as well as in the postmortem room, and Figure 2 represents our impression of what we found in relation to this. On looking at the diagram it is rather disconcerting to see that the attachment of the base of the septum to the annulus fibrosis, between the pulmonary and aortic valves anteriorly, and the tricuspid and mitral valves posteriorly, is curved. However, we have found practically, that to follow this line and place a foreign body or suture, in this line, is not as difficult as might appear, especially is this so when there is a hiatus and consequently the curves are not present. (Fig. 3.) The other problem which arose in placing such a suture was the possible presence of a dextraposed aorta. So far picking up the annulus fibrosis between the aortic and pulmonary rings in order to seal off completely the right margin of the dilated base of the aorta which is seen in Eisenmenger's disease has not been accomplished. However, with a suture well placed, it was hoped that it might provide useful occlusion.

There probably is more of a safety margin between the mitral and tricuspid valves than might appear on theoretical consideration. The septal cusp of the mitral valve when open, does not lie closely against the inter-ventricular septum, but the septal cusp of the tricuspid lies more closely to the septum during diastole. (Fig. 2.) The attachment of the chordae tendineae to papillary muscles leaves a moderate space, probably up to half an inch, between them, through which there is room to work with little danger. We have had little difficulty in passing this area.

(3) Regarding the bundle of Hiss, there are many excellent dissections including those by Professor Grant and Dr. Mahanti, showing the course of this bundle. It arises posteriorly in the wall of the right auricle, traverses the annulus fibrosis and is directed forward and downward, posterior to, then below or, in the margin of, the membranous septum. In some congenital hearts, with a patent septum, the bundle was found to lie in the existing muscular portion posterior to the hiatus. At its origin it lies beneath the endocardium on the right side of the septum in the position indicated. As it passes distally beneath the pars membranacea septi, it divides into right and left bundles, the left passing through the substance of the muscular portion of septum to reach the plane beneath the endocardium on the left side of the septum from whence it courses to the musculature and papillary muscles of the left ventricle.

An instrument or suture passed through the heart, as described, necessarily crosses almost at right angles to the course of this bundle, and it, of course, must not be injured. The instrument and suture should pass in the direct line of the septum or slightly to its left to avoid the bundle as it lies beneath the endocardium on the right surface of the septum. Neither in our experimental work nor in the clinical patients operated upon, has there been evidence of ill effects produced by injury to the bundle of Hiss. Figure 4



shows and interventricular septum looked at from the left ventricular surface and No. V looked at from the right ventricular surface, indicating the course of the bundle of Hiss, in relation to the pars membranacea septi and the muscular portion of interventricular septum.

The interauricular septal defect also presents a challenge, but it is much less difficult to meet than is the interventricular defect, chiefly because the structures in relation to the field are easier to avoid.

Usually an interauricular septal defect is a persisting foramen primum and not foramen ovale. If giving symptoms or cardiac enlargement the defect is large. It causes ill effects by allowing left auricular blood which has just returned from the lungs to flow into the right auricle from which it again goes to the lungs with unsatisfactory completion of circulation. The ingenious method described by 'Cohn<sup>2</sup> of San Francisco has worked very well in experimental animals in their hands, and can be applied quite satisfactorily to small septal defects between the auricles. However, small septal defects probably cause few clinical symptoms, and their method would be difficult to apply in larger septal defects and in those in which the septum is practically missing.

In about 30 animals we have passed sutures through in the line of the interauricular septum beginning at the site of the transverse sinus behind the aorta, and coming out posteriorly between the superior vena cava and the right pulmonary veins. With two, three or four sutures through in this way, pulled taut, tied together posteriorly and then tied anteriorly, we have been able to compress the anterior to the posterior wall of the auricle in such a way as completely to occlude the defect. It has the other advantage of diminishing the size of the enlarged auricles. On examination of specimens, the anterior wall of auricles has healed to the posterior wall in such a way as to cause complete occlusion of the defect and construction of what appears to be another interauricular septum.

#### CASE REPORTS

**Case 1.**—C. G.: The first patient operated upon was a child of 17 months. There was fairly marked cynaosis and moderate clubbing. The child had not walked and had so little energy she would sit only when supported. The mother described a persistent cough and sputum, which was shown at operation to be related to atelectasis of the whole left lung. The heart was greatly enlarged. (Fig. 6.)

*Operation.* Cyclopropane was supplemented by continuous intravenous of one-tenth per cent novocaine solution. Exploration was made through the second left intercostal space down the middle of the sternum and out through the sixth space. On opening the pericardium one per cent novocaine solution was sprayed over the surface of the heart. A suture was passed through the apex of the left ventricle. Apart from extra systoles, there were no untoward effects. The heart was then dislocated forward and examination of the posterior surface carried out without difficulty. During this, the heart became more blue, and there seemed to be some embarrassment of its action. However, on allowing it to return to its normal position, it recovered its poise and normal action. The heart was about two and one-half to three times normal size. It showed some cyanosis. The right

## CLOSING EFFECTS IN CARDIAC SEPTA

ventricle was enlarged and appeared to be roughly equal to that of the left. The pulmonary artery was greatly dilated and had high pressure; on palpation it felt equal to that of the aorta. The coronary vessels appeared normal.

A strip of fascia lata about three-quarters of an inch in width and six inches in length with a good blob of tensor fascia femoris muscle on the upper end, was removed. Through the other end a silk suture was attached. This was threaded on a straight sewing needle four inches in length.

A point was selected on the anterior surface of the heart, above and slightly to the right of the descending branch of the left coronary artery, just distal to the annulus fibrosis. Here, one per cent novocaine solution was injected, making

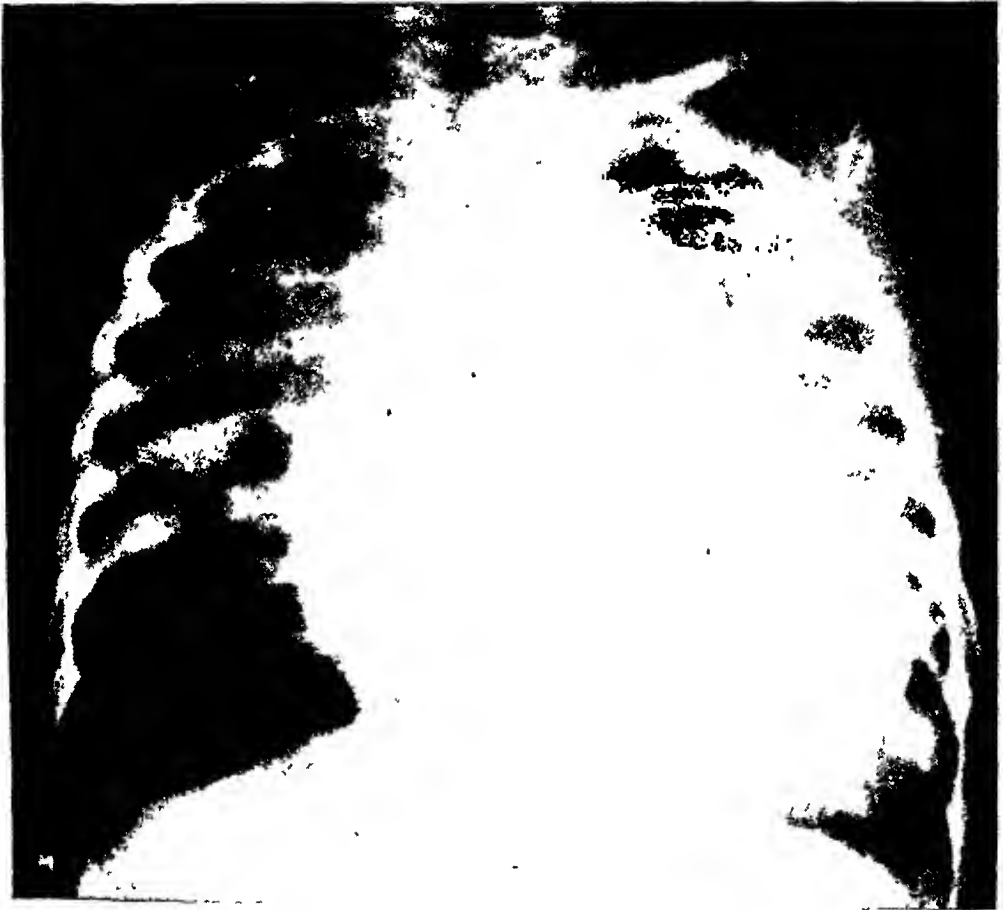


FIG. 6.—Röntgenogram showing size and shape of heart in child 17 months of age.

a bleb beneath the epicardium. With the threaded needle reversed, it was passed through the anterior wall of the heart, at the point mentioned. There were some extra systoles, but no other disturbance of the heart action. When the blunt end of the needle had passed through the wall of the heart, it felt as if it were in a cavity and not in the substance of the septum. On palpation with this needle, as with a probe, it was found to be in a fair sized hiatus measuring about 1.5 cm. It was passed across the hiatus until an obstruction was met at the posterior surface. Then on swinging the heart forward, by traction on the apex, and with the finger posteriorly, the end of the needle could be felt, like the end of a probe through the heart muscle posteriorly. The right position was then selected and the needle passed on through the posterior wall appearing through the epicardium. There was no injury to coronary vessels or coronary sinus. By the time this was completed, the heart became moderately cyanosed and showed some irregular action. However, on allowing it to go back into its normal position, with the needle

still through the heart, the heart regained its regular action and poise. The cyanosis which had appeared, diminished and the blood pressure remained normal. The needle was left in situ, through the heart for several minutes, to see if there was any interference with mitral or tricuspid valves, or any other ill effect. The cardiac conduction appeared to be normal. The needle was then drawn through posteriorly and with it the silk and living suture. Again this was held lightly in position, by slight traction on the posterior end, to observe any ill effects. If necessary we could, at any moment, remove the suture. However, there were no ill effects. Traction on the suture was increased, causing it to tighten across the hiatus, and almost immediately there was some improvement in the appear-



FIG. 7. Age 11—Patent interventricular septum.

On left—before operation.

On right—ten days post operation shows some inflammatory oedema at lung hilus, also change in size and shape of heart.

ance of the heart. Its size, particularly of the right ventricle, diminished quite considerably. The color of the heart improved and there seemed to be no ill effects. The anesthetist found no change in the patient's condition or blood pressure. It was thought, therefore, that perhaps the suture was in a satisfactory position and was performing some useful function. While moderate traction was applied to the posterior end of the suture, it was stitched to the epicardium at several points, avoiding branches of the coronary artery. This moderate tension caused some anteroposterior compression of the heart at the site of the hiatus. The mass of muscle in the anterior end of the suture, plugged the anterior opening in the heart satisfactorily. There was practically no hemorrhage and the patient stood the operation very well. The pericardium was repaired and the chest closed.

Case 2.—W. L., age 11: The patient was not cyanosed but had little energy. Examination showed an enlarged heart. He was operated upon through an exposure similar to the above. The heart was about three times normal size. A

living suture was passed through in a fashion similar to that described. The patient stood the operation very well. There were no ill effects whatever. On tightening the suture in position, there was marked diminution in size of the heart with improvement of its color. Blood pressure which was 120 systolic at the beginning, during the operation fell to 108, but by completion of the operation had returned to 120.

The patient made an uninterrupted recovery. On the fourth day he was given heparin for a period of seven days, keeping his clotting time between eight and 14 minutes. The result seemed to be quite satisfactory, although the late result cannot be determined as yet. Figure 7 shows the heart roentgenograms before and 10 days after operation.

**Case 3.—BB., age 13:** This patient was operated on quite satisfactorily with similarly good results.

Two other patients were explored hoping to carry out a similar procedure. However, in both of these, transposition of great vessels was discovered which had not been revealed with certainty by clinical, radiographic evidence or by catheterization of the heart. In these no interferenc with the heart was carried out.



FIG. 8.—Patent interauricular septum.

On left—before operation.

On right—Two weeks following operation showing change in size and shape of heart.

#### ~ INTERAURICULAR SEPTUM

**Case 4.—C. W., age 12:** This patient was operated upon through a similar exposure, for a patent interauricular septal defect as well as what was thought to be a smaller patent interventricular septal defect. At operation the right auricle was found enormously enlarged, probably ten times the size of the left. The auricular appendage was at least ten times as large as that on the left side. The ventricles, while enlarged, were small in comparison with the enormously enlarged right auricle. By means of the enlarged right auricle, the heart was already rotated very much to the left so that the aorta appeared on the right

side of the pulmonary artery. It was decided, therefore, to place our sutures of silk, in this case, beginning to the right of the aorta and pulmonary artery and emerging posteriorly through the area between the superior vena cava and the right pulmonary veins. Two sutures were passed through without difficulty. (It is the plan in future cases to pass more than two sutures.) These sutures were tied together posteriorly and were drawn taut from the anterior end and compressed with the finger. This caused a very great change in the size, shape and color of the heart. The right auricle diminished to at least one-half its size within about two minutes. The patient's general condition was good. The blood pressure remained normal. The sutures, after experimenting with this for some time, were tied down firmly, compressing the anterior and posterior walls of the auricles. This caused continued improvement in the patient's condition. The chest cavity was then closed without drainage. (Fig. 8.)

The patient made an uninterrupted recovery. From the fourth to the 11th day she was given heparin<sup>4</sup> to prevent propagating thrombosis from the area of suture. She made a good recovery and her general health is much improved. As there was very little cyanosis before, there was little improvement on this account.

One of these patients undergoing operation for interventricular septal defect died. Examination showed that the patient died not of any ill effects in the heart or at the site of operation. The atelectasis of the left lung was thought by the pathologist to have been responsible for the death, and this would be borne out by the clinical course of the patient toward the end of the first postoperative week, which time she survived. The suture going through the heart was in good position and seemed to be in a position to occlude to a degree the patent interventricular septum.

#### CONCLUSIONS

The cardiac septal defects present a challenge to the surgeon. Attempts at closure, at least in part, have been carried out experimentally, and in clinical patients resulting in moderate improvement. This would suggest further work which might go on to produce better effects anatomically and clinically. The demonstration that this can be done with safety is probably the chief feature of the present work.

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- <sup>3</sup> Murray, Gordon; F. R. Wilkinson, R. MacKenzie; *Reconstruction of the Valves of the Heart*; *Canadian M. A. J.* 38: 317-319, 1938.
- <sup>4</sup> *Amer. Jour. Med.*

DISCUSSION.—DR. ARTHUR H. BLAKEMORE, New York: I certainly enjoyed this presentation. I heard via grapevine what was going on in Toronto and I congratulate Dr. Murray. Some years before the war, I think in 1939, we did some experimental closures of the septa in dogs, that we had made by a punch. We were rather interested in seeing how well simple inversion of the auricular appendage worked when pushed through the opening and, after getting it in there, packing in some fascia lata to make it a self-retaining ball on the other side of the septum.

I should like to ask Dr. Murray what kind of needle he used and also would like to know how tight he drew the interventricular septal sutures.

DR. ALFRED BLALOCK, Baltimore: You all remember the amazing paper on coronary occlusion presented by Dr. Gordon Murray at the last meeting of this Association, and now he comes forward with an even more amazing presentation. Certainly it never would have occurred to me to place sutures blindly in this manner. I did not understand, Dr. Murray, what type of suture you used other than that it was a living suture. I would like to ask further about embolism, if there has been evidence in your experimental or clinical work of that. I take it that a good part of the occlusion of such a septum is from the thrombosis which occurs on the suture material.

(slides) I would like to describe a new method for creating an inter-auricular defect. This method was devised by Dr. Hanlon and myself and the advantage of it is that it can be done under direct vision and without excessive blood loss. The ability to carry it out depends on the fact that the pulmonary vein is attached to the posterior wall of the right auricle. In this diagram you can see that part of the right auricle, together with the pulmonary vein immediately posterior to the auricle, is occluded by an especially devised clamp. An opening is made in the pulmonary vein and a similar opening in the right auricle. The posterior segment of the auricle is adherent to the anterior wall of the pulmonary vein, so one can simply excise a segment of the two walls; in fact, one can pull an additional quantity of this septum out and excise it. The closure consists simply of suturing the anterior part of the auricle to the anterior segment of the pulmonary vein, it being unnecessary, of course, to place any sutures posteriorly.

We have used this method on only one patient, and that only ten days ago. This was a child with transposition of the great vessels. The postoperative result is good thus far, although it is too early to know the eventual outcome.

Again I wish to congratulate Dr. Gordon Murray on his excellent work.

DR. D. W. GORDON MURRAY, Toronto (closing); Regarding Dr. Blakemore's discussion about needles, we use skin needles with the rough edges and the point removed, or ordinary seamstress needles of the larger variety. Wood needles for darning or for petit point work are good. Any of the needles are used in reverse, putting the eye through first, using it much as one would a probe. With this the front wall of the heart, then the hiatus, then the posterior wall can be felt quite satisfactorily.

Regarding the tension applied to the suture through the interventricular defect, it is pulled sufficiently that a bit of a dimple appears on the anterior wall where the knot on the end of the suture comes against the wall of the heart. By holding the end posteriorly, one can feel if anything else, such as a valve or chordae tendineae, may be tugging on it, much as a fisherman feels a bite on a hook in the water. If satisfactory, it is then stitched down to the epicardium front and back. In the one case examined at postmortem, the suture was in satisfactory position and seemed to be under satisfactory tension.

Regarding Dr. Blalock's question about the type of sutures: For the inter-ventricular one, we use a living suture removed from the fascia lata of the thigh. This is of fair size, so that by its bulk it will partly fill the opening in the hiatus. While we have not used more than one, probably several could be applied to more or less produce a basket weave to more or less fill the hiatus.

For the inter-auricular septal defect, linen, cotton or silk sutures are used. With these the front wall of the auricle is drawn down and sutured to the posterior wall.

So far as embolism is concerned, this is controlled by the use of heparin. We hesitated to give heparin immediately. However, on the second or third day, heparin has been administered so that any thrombosis that might have occurred up to that time, would then be limited and allowed to heal in position. There has been no evidence of extensive or dangerous thrombosis, and no embolism in any of these patients.

# REVASCULARIZATION OF THE HEART \*

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## INTRODUCTION

IT IS AGAIN MY PRIVILEGE to present investigations on revascularization of the heart. The work done by us in the period between 1932 and 1942 has been reported. Briefly stated, we showed that the heart could be revascularized in two ways. One of these was by the production of extra coronary anastomoses, i.e., communications between the coronary arteries and the blood vessels of tissues grafted upon the heart. The other method for revascularization was by the production of communications between the various coronary arteries so that one artery connected with another. This was accomplished by the production of inflammation on the surface of the heart. These methods were effective to the extent of reducing by 50 per cent the mortality that occurred after ligation of the descending ramus of the left coronary artery at its origin. Thirty-seven patients with severe coronary artery disease were operated upon using these methods and the clinical results confirmed the experimental studies.

Since February 1945 my associates and I have been attempting to revascularize the heart by converting the coronary sinus into an artery. The results of this work up to February 1947 were recently published.<sup>1</sup> It is my purpose to present this work to this association. A number of investigators are now working on the coronary problem and no doubt our experiences will be an aid in their work.

## DISCUSSION

The coronary sinus. This is a vein that lies in the auriculoventricular groove of the left ventricle. (Fig. 1A.) It carries blood from the left ventricle and empties into the right auricle on the posterior aspect of the heart. The sinus can be ligated with little or no mortality. After it has been ligated blood drains directly into the four chambers of the heart. The sinus is then available and can be used for the entrance of oxygenated blood to the left ventricle. The wall of the sinus becomes thickened after it has been ligated. The sinus and its tributaries can tolerate arterial pressures.

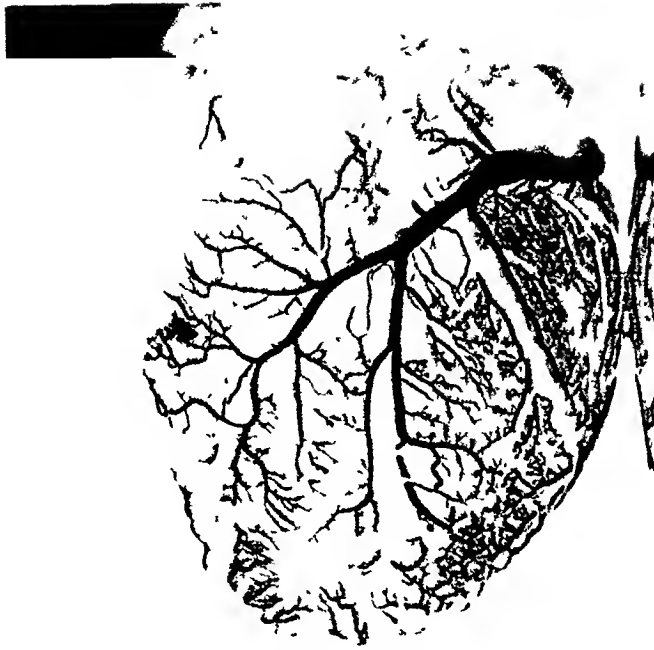
*The Artery for Anastomosis to Sinus in the Dog.* The only artery in the dog that was large enough and long enough for anastomosis was the common carotid. We used the left carotid artery. It was dissected free throughout its course; it was transected below the bifurcation and it was turned down into the chest. The technique of anastomosis is shown in Figure 2.

*New Branch from the Aorta.* The common carotid artery is larger than the coronary arteries. No doubt it is larger than necessary. In man the

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\* Read before the American Surgical Association May 29, 1948, Quebec, Canada.

A



B

PLATE I. A.—Anterior view of human heart. Coronary sinus and coronary arteries were injected. The venous system is white; the arterial system is red.

B.—Posterior aspect of dog heart. Common carotid artery was used for anastomosis to coronary sinus. Carotid artery and coronary sinus injected in white; coronary arteries injected in red.





carotid artery frequently cannot be sacrificed without cerebral complications. In the dog it can be taken almost as a routine provided the bifurcation is preserved. The dissection of the carotid artery in a patient with coronary artery disease would add considerably to the magnitude of the operation. For these reasons it was necessary to consider other possibilities to obtain arterial blood. A pulmonary vein was considered but we did not believe the pressure was high enough in this vein to produce adequate flow. A new branch from the aorta appeared to be the best possibility. (Fig. 3.) The aorta lies in close proximity to the sinus. It is about three centimeters from the sinus. The

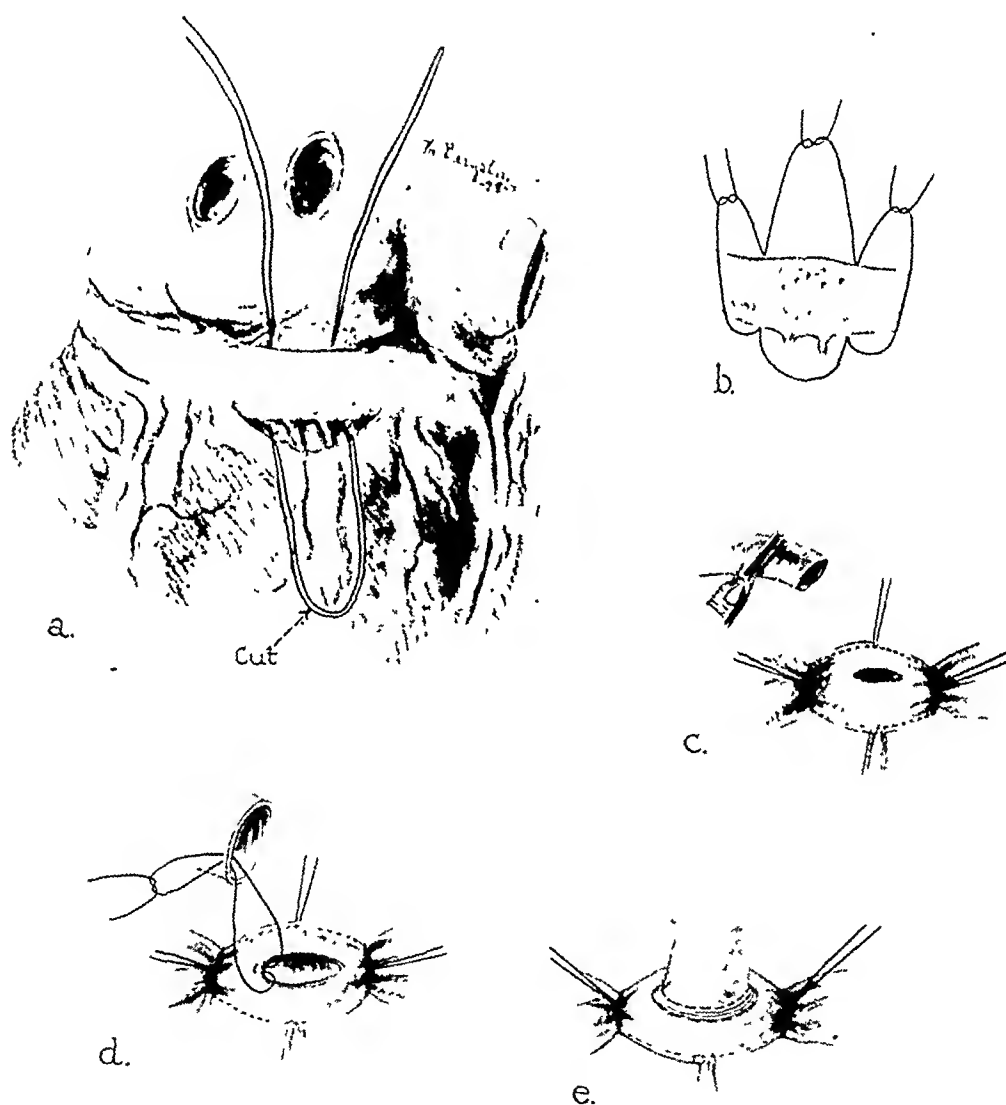


FIG. 2.—Anastomosis of left common carotid artery to coronary sinus in the dog. (a) and (b) show method for isolation of segment of sinus so that it can be opened without hemorrhage. The sinus is partially dissected free. A carrier with two silk sutures is passed beneath the sinus at two points as indicated. One piece of silk is cut. A proximal and a distal ligature and a mattress suture are thereby provided. These are tied as in c and the sinus is opened. Four cardinal everting mattress sutures are placed between sinus and artery as shown in (d). The anastomosis is completed by a continuous everting suture as in (e). Trauma to sinus is minimal to prevent thrombosis. (J. A. M. A.).

Pott-Smith-Gibson clamp enabled us to open the aorta and to make anastomosis to the aorta. In patients with extensive arterial disease it will be desirable to select a segment of aorta that is free of disease. A free graft of vein or artery was used in our experiments. We used a free graft of brachial artery in one patient upon whom this operation was done. This artery had atheroma

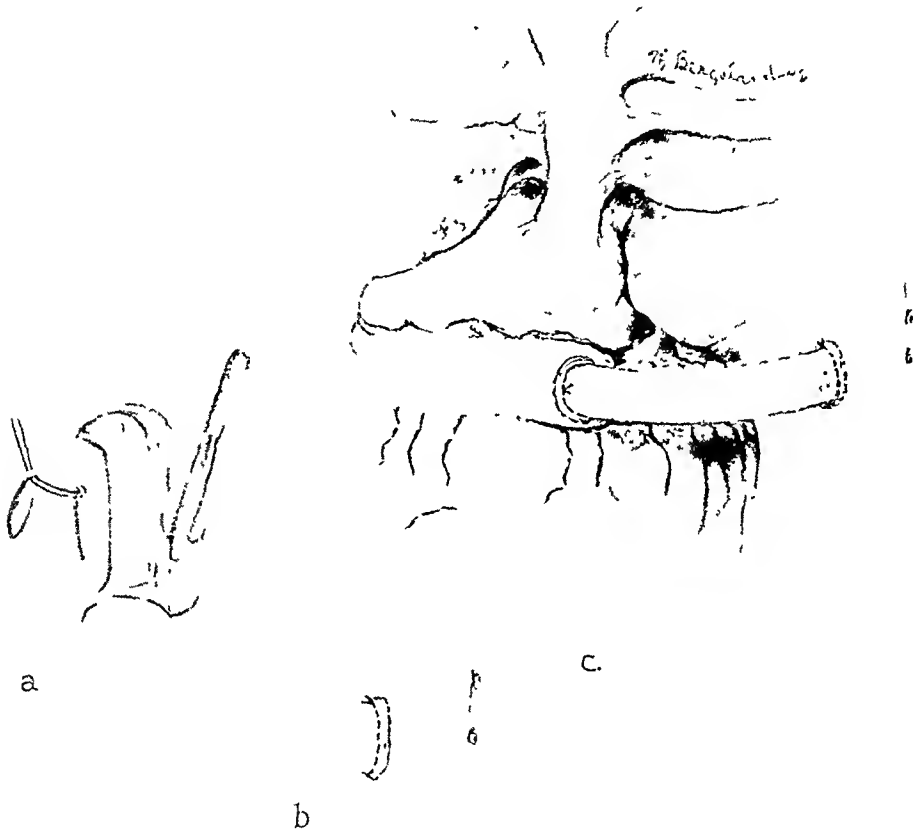


FIG. 3.—Free graft of vein between aorta and coronary sinus of the dog. The aorta is dissected free for a distance of about 3 cm. Two intercostal arteries are cut. The special clamp is placed on aorta as in (a.) allowing some blood to pass the clamp. The aorta is opened by incision about 5 mm. in length. An everting mattress suture is placed between graft and aorta at each end of this incision. Anastomosis is completed by a continuous everting suture as in (b.) (c.) shows the complete operation.

in its wall. It appears that a vein is preferable to artery and we are using vein grafts at the present time. Observations of the grafts will be made in experiments that have gone along one or two years.

Recently we found that the size of the graft was a factor in the success of the experiment. We made incision in the aorta about 5 mm. in length.

We used a graft of jugular vein. The incision in the sinus was about 5 mm. in length. After the anastomosis was completed we found that the heart did not always tolerate the anastomosis. Frequently failure developed as the chest was being closed or within 24 hours. At the present time we are constricting the graft of the jugular vein so that it will be about the same size as that of the carotid artery. This is done by placing a ligature of silk around the vein so that the inside diameter is about 3 to 3.5 mm. We found in the dog that the heart tolerated the current delivered from the common carotid artery. No doubt there is an optimum amount of blood for the heart. It is possible to deliver too much blood to the heart.

In so far as I know this is the first time a new branch from the aorta has been made. This anastomosis has several advantages. The aorta and the sinus are in one surgical field. The technic is not difficult. There are problems of thrombosis on which we are working at the present time. We expect to determine patency by exploration after the anastomosis has been made and keep about 25 dogs with patent anastomosis for one to three years for observation in long term experiments.

*Preparation of the Sinus for Anastomosis.* Anastomosis to the normal sinus in the dog was possible in the occasional experiment. As a rule the normal sinus in the dog was so delicate that sutures could not be placed without tearing the sinus. We found that ligation of the sinus resulted in some thickening and fibrosis of the wall of the sinus. This made it possible to place sutures more satisfactorily. In most of the experiments changes in the sinus were continuous and after several weeks the sinus was small and the wall fibrotic. The optimum time for anastomosis was 8 to 14 days after ligation. Occasionally the sinus was satisfactory for anastomosis six months later and there appeared to be variation in the fibrous thickening.

*Measurements of Benefit.* In view of the technical problems that had to be overcome in order to develop this operation we were particularly desirous to know whether the anastomosis was beneficial. We spent 18 months working on this project before we had any definite evidence that it would be beneficial. We now have an answer to this aspect of the project. The anastomosis is beneficial and the degree of benefit appears to be significant.

Measurements of benefit were made by complete ligation of the descending ramus of the left coronary artery at its origin and then determination of results. In a normal control group of dogs ligation of this artery was followed by early death, i.e., within 24 hours in 7 out of 10 animals. Only three recovered. In another group of dogs with patent anastomosis between carotid artery and coronary sinus ligation of this artery was followed by no early deaths in 10 animals; there were two delayed deaths, one after 8 days and one after 13 days; the remaining eight animals continued to live.

The amount of destruction in myocardium was equally significant. In the three animals of the control group a large infarct was present in each specimen. The destruction of myocardium involved the entire thickness of myocardium

(Fig. 4.) In the group with patent anastomosis the destruction of myocardium was absent or slight. In this group all 10 dogs lived so that there were 10 specimens for examination whereas in the control group there were only three specimens for examination. Out of the 10 there were four that showed no infarct, and in the remaining six the destruction of myocardium was not extensive in any specimen. (Fig. 5.)

These two measurements of benefit—mortality and infarction—indicate that the anastomosis can and does supply the myocardium with a significant quantity of arterial blood. It would appear that the anastomosis enables one to ligate a major artery with little or no mortality and with little or no infarction.

*Effectiveness of this Circulation.* The measurements of mortality and infarction after coronary artery ligation indicate that arterial blood in the

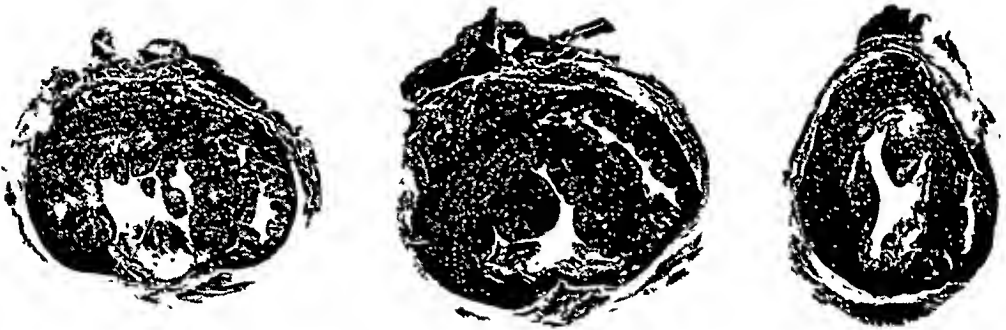


FIG. 4.—Infarcts in the control group. The descending ramus of the left coronary artery was ligated in a group of 10 dogs. Only 3 animals survived this ligation and each of these specimens showed a large infarct. Compare with Figure 5.

venous system is an effective functional circulation. These measurements can be regarded as proof of the effectiveness of this circulation. Additional information on this point was obtained by injection studies of dead specimens. The dog was bled; the blood was heparinized and the heart was removed. The coronary sinus was cannulated as was also the left coronary artery. Blood was injected into the sinus under pressure of 120 mm. mercury. The amount recovered from the artery was measured. In normal hearts the average amount recovered from artery was 9 cc. per minute. In another group of experiments the coronary sinus was ligated and several weeks later similar determinations were made. The average amount recovered from the artery was 22 cc. per minute. On the basis of these experiments it would appear that blood can enter the arterial bed from the venous bed. It would also appear that larger quantities of blood can enter the arterial bed after the sinus has been occluded. This point may have significance in reference to the functional characteristics of retrograde flow. Does this arterial blood in the venous system have the same functional possibilities in reference to oxygen-exchange

## REVASCULARIZATION OF THE HEART

as does blood in the arterial system? Does any of the arterial blood from the venous side by-pass the capillary bed and escape into the chambers of the heart without giving up its oxygen? We have no studies on this subject. It is possible for blood to by-pass the capillary bed by another route. This



FIG. 5.—Infarcts in group with anastomosis between artery and coronary sinus. The descending ramus of the left coronary artery was ligated in a group of 10 dogs. There were no immediate deaths after this ligation. In 4 specimens there was no infarct. In the other specimens destruction was minimal and appeared in scattered areas. In no specimen was extensive destruction of myocardium found as occurred in each of the control group. Each specimen in Figure 3 and Figure 4 is mounted in the same relative position. The infarct is inferior and between left and right ventricles. The grafted artery can be seen in several specimens. In the middle specimen of the bottom row a scar is seen anteriorly. This occurred because the circumflex ramus of the left coronary artery was accidentally ligated at the time of anastomosis. The small infarct following ligation of the descending ramus of the left coronary artery lies opposite this scar in a papillary muscle.

is by way of the superficial veins that drain directly into the right auricle. There are a number of such channels under the epicardium of right ventricle both anteriorly and posteriorly. The anastomoses between these veins and the coronary sinus system are variable. In some normal hearts they may be absent; in others there are numerous connections. After ligation of sinus these communications usually, but not always, increase. We injected and cleared approximately 30 specimens after arterialization of the sinus and in about half of the specimens these communications were abnormally developed. In two specimens these communications resembled arteriovenous fistulae. These veins could be ligated at operation when anastomosis is done. We expect to get evidence in favor of ligation of these veins. Perhaps a row of superficial sutures around the right auricle may be necessary to prevent further development of these veins. The usual appearance after arterialization is shown in Figure 1B.

*Application to Patients.* One patient was operated upon. This patient, a man 45 years old, had angina pectoris for five years. He was almost totally incapacitated. Electrocardiogram did not show evidence of an infarct.

Operation was done January 27, 1948. A segment of left brachial artery was used for the graft. The graft had some atheroma in the wall. The aorta was markedly dilated. Anastomosis was made between aorta and graft. The pericardium was adherent to the heart. It was separated from the sinus. Dissection of the sinus was carried out. Stabilizing sutures were placed in the pericardium. The heart beat became weak and blood pressure could not be obtained. Adrenalin was given and heart action improved. The operation was continued. The sinus was dissected from the heart for a distance of one centimeter. An occluding ligature was placed on the sinus toward the ostium. A temporary ligature was placed on the other end of the segment of sinus. The sinus was opened. Anastomosis was carried out between artery and sinus. The heart became weak and blood pressure could not be obtained while the anastomosis was being done. Anastomosis between aorta and graft was completed. The clamp was removed from the graft. The heart beat became stronger after arterial blood entered the sinus.

After the operation was completed the blood pressure rose from 60 mm. mercury to 124 mm. mercury. The patient became conscious. Circulatory failure developed. Death occurred after 24 hours.

Autopsy examination showed recent infarct of posterolateral and basal aspect of left ventricle; arteriosclerosis of aorta; arteriosclerosis of coronary arteries moderate to marked with focal stenosis. Fluid was injected through the graft from aorta into coronary sinus. The anastomosis was patent.

I believe the recent infarct contributed to the cardiac failure. This infarct probably formed during the anastomosis to the sinus when the blood pressure was low.

SUMMARY

1. A third method for revascularization of the heart is presented. This method consists of arterialization of the sinus.

2. Arterialization of the coronary sinus was accomplished by grafting a systemic artery into the sinus and also by making a new branch from the aorta to the sinus using a free graft of artery or vein.

3. Arterialization of coronary sinus is effective physiologically. After anastomosis has been made it is possible to ligate a major coronary artery with little or no mortality and with little or no infarction.

4. Various problems concerning circulation in the heart invite further study.

5. One patient with severe coronary artery disease was operated upon. A free graft of brachial artery was placed between aorta and coronary sinus. A fresh infarct developed in the interventricular septum probably at the time of operation. The anastomosis was patent at the time of death one day later.

I believe we are approaching the time when the operation can be applied to patients. Dr. Gallie in his presidential address, in discussing new operations used the phrase "a large amount of good and a small amount of harm." It is our hope that further experience in application to patients will fall within the broad meaning of his statement.

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DISCUSSION.—DR. B. NOLAND CARTER, Cincinnati: Dr. Beck's work concerned with surgery of the heart has been not only of great interest to me but has been a most helpful stimulus as well. I did not realize, until I became interested in cardiac surgery, how much fundamental work had come from Dr. Beck's laboratory. No matter what phase of cardiac surgery my group embarks upon, they find that Dr. Beck has already explored the field and made important contributions to it. I have enjoyed his paper today, but not having had experience with the latest operation which he has dealt with, I am not in a position to make pertinent first hand comments concerning it. It is certainly a brilliant technical feat, and one which may well lead to easier and less arduous means of bringing in a new supply to the heart by way of the coronary sinus. The operation is of such recent origin that I feel sure that many questions concerning it which have occurred to Dr. Beck have not had time to be answered. Among those are: (1) How to regulate the flow of a proper amount of blood to the heart; too much might be as harmful as too little. (2) How is venous drainage effected if the venous bed is filled with arterial blood? (3) What will be the result of the production of an A-V fistula so close to the heart? (4) How will patients with severe myocardial damage tolerate this technically difficult procedure?

I have become especially interested in attempting to produce a new blood supply to the myocardium by utilizing the lung as the source. The proximity of the lung to the heart and its extreme vascularity have appealed to me as factors which should make it particularly suitable as a source of blood supply to the heart. The obvious disadvantage of utilizing the lung in this fashion is that the pressure within the pulmonary circulation is so much lower than that in the systemic one. On the other hand, if one is dealing with coronary sclerosis, the pressure in the smaller



terminal vessels in the myocardium is thought to be quite low also and, therefore, could well be fed blood from the pulmonary circuit even though the pressure in the latter is low.

Soon after embarking on the problem of utilizing the lung as a source of blood supply to the heart, I found that Lezius, a German surgeon, had done considerable work along this line in 1939. In brief, our procedure consists in making a large window in the pericardium, painting the surface of the heart and the under surface of the lung with asbestos powder, and suturing the lung to the edge of the pericardial window. In this way, the two surfaces are held in apposition by the sutures in the pericardium and the irritating effect of the asbestos powder, as described by Beck, produces vascular adhesions between the two surfaces. The results of our experiments are shown in the slides.

The operation was performed on 12 normal dogs which were sacrificed at varying intervals. The heart and lungs were removed and a mixture of dogs' blood and india ink was injected at normal pressure into the pulmonary artery of the adherent lobe. Particles of ink were found regularly in the myocardium, but particularly in the superficial vessels.

In the second group the coronary artery was ligated following cardiopneumonopexy; the dog was sacrificed, and injection made. Here the ink was found well distributed throughout the myocardium, as indicated on the slide.

I feel that without doubt we have shown that vascular connections can be made between the vessels in the lung and those in the heart. We have not proven, however, the direction of blood flow nor the volume of blood conducted by the new channels. There was a striking difference between the amount and distribution of the ink in those cases in which ischemia had been created by ligation of the coronary artery versus the normal cases. This bears out the theory that an organ in need of blood will obtain it through any available source.

Feeling that it is not only justifiable but desirable to apply proven laboratory procedures to human cases, I have operated on two patients, utilizing the above procedure. The first patient was operated on about one year ago and has been strikingly improved, so that he no longer considers himself incapacitated. The other patient unfortunately died 36 hours after operation from an overwhelming infection.

I would like to say in closing how much I have enjoyed Dr. Beck's film, and to congratulate him on a splendid piece of work.

DR. ALFRED BLALOCK, Baltimore: I want to discuss the very interesting work that Dr. Beck has reported. I am sure you know that this problem is being studied in many laboratories since Dr. Beck pioneered in this field. For example, in Canada, Dr. Reppstein in Montreal has been conducting such experiments, and Dr. Stenstrom in Victoria, B. C., is carrying out similar work.

Dr. Thomas Johns and I have performed a moderate number of operations in which the carotid artery was brought down and anastomosed to the sinus, as Dr. Beck has described. In 52 experiments the carotid artery was used. In 47 of these the anastomosis was open at the completion of the operation: in 28 of the 47, an end-to-end anastomosis was performed, and I believe Dr. Beck described that as the method he used; in the remaining 19 an end-to-side anastomosis between the end of the carotid artery and the side of the coronary sinus was performed. Of the 28 animals in which end-to-end anastomosis was performed, 57 per cent died within 72 hours of operation; the anastomosis was patent in most of them at the time of death, and there was marked engorgement of the superficial third of the muscle of the left ventricle and the adjacent part of the right ventricle. Of the 12 animals out of 28 who survived the end-to-end anastomosis for a longer period than 72 hours, there was thrombosis at the time of autopsy, in 10 of the 12.

It looks as though most of the animals die unless thrombosis occurs. In other words, as Dr. Carter has intimated, it may be that the carotid transports too much blood.

Turning to the end-to-side anastomosis, in which the blood could flow to the right auricle, 16 of the 19 animals survived for an extended period. At the time of autopsy the anastomosis was thrombosed in 10 of the 16. In five of the six, all the blood seemed to be going into the right auricle instead of in retrograde fashion. In the remaining one of the six, the sinus had become occluded just before its entrance into the auricle and backward perfusion was taking place. Thus, in these two groups of end-to-end and end-to-side anastomoses, there were only three in which backward perfusion of the sinus was occurring, and I would like to show slides of the autopsy appearance of these three. The coronary sinus was markedly dilated and thickened in these three cases.

An effort was made in five experiments to conduct arterial blood to the coronary sinus by using a plastic tube, one end of which was placed in the left ventricle and the other in the coronary sinus. In one of these, the tube was observed to be conducting blood 72 hours postoperatively. In the others, allowed to go a longer time, thrombosis occurred.

I think one must conclude that even if this type of shunt or bypass operation is proved to be sound from a physiologic viewpoint, one should hesitate to use it clinically because of the technical difficulties and the associated high mortality.

DR. SAMUEL A. THOMPSON, New York: I should like to take this occasion to state that the work we have done was stimulated originally by Dr. Beck. We have just completed the follow up study of the surgical treatment of coronary disease in a series of patients, some of whom were operated on almost nine years ago.

We prefer to consider this method not so much as a surgical treatment of angina, but as a surgical rehabilitation of the coronary cripple, especially since all these patients were more or less completely incapacitated and were actually cardiac cripples. The criteria we use to determine the degree of rehabilitation are (1) Relief of angina or pain; (2) increase in exercise tolerance; (3) ability to take care of their daily needs so that ordinary moving and travel is possible; (4) return to their former occupation or at least a gainful occupation.

The method consists in the intra-pericardial use of U.S.P. talcum powder, and by this method we produce a collateral circulation to the heart which is both intra- and extracardiac, by the establishment of pericardial adhesions, plus myocardial hyperemia. This myocardial hyperemia is the result of the talcum foreign body reaction, and is a prolonged hyperemia. So far as we can determine it is a form of talcum powder granuloma, and the characteristics of any granuloma are an increase in the number of capillaries and hyperemia. This, of course, is just the reverse of the myocardial ischemia which occurs in coronary disease. These granulomas last for many years.

The degree of rehabilitation does not occur equally in all patients. In this series of 38 patients, in more than 70 per cent the results were good to excellent; in four of the 38 patients the results were less than 33 per cent improvement, which we classify as poor.

The operation is extremely simple. A portion of the fifth left costal cartilage is removed, the pericardium is opened, the pericardial fluid is aspirated and the talc is widely distributed over the epicardium. The wound is closed without drainage.

The need for rehabilitation becomes apparent from a study of the vital statistics. In 1945, the total death rate in the United States was approximately one and one-half million; almost 30 per cent of these were cardiac deaths, which is the No. 1 killer, and almost 10 per cent, or about 130,000 deaths occur from coronary disease and angina. Not all these coronary deaths were previously crippled, for about 15 per cent

died with the first attack, but it is fair to assume that a large percentage were moderately to severely incapacitated before death.

DR. CLAUDE S. BECK, Cleveland: There is much that I should like to say but the hour is getting late. Dr. Carter has raised several questions I should like to try to answer. The first question is whether or not too much blood might be delivered to the heart by the new artery. I think we might take a moment to consider the significance of this question. Indeed, with coronary artery disease in the past the important point always concerned too little blood to the heart. Now we are confronted with the possibility of delivering too much blood to the heart. This is indeed a matter of great significance. Can we get too much blood to the heart? The answer to this question is that it does seem possible to deliver too much blood to the heart. The amount of blood delivered by the graft of jugular vein, as shown in the motion picture, was too much to be tolerated by the heart. In the past months we have learned that the jugular vein graft must be constricted so that its inside diameter is about 3.5 cm. It would appear that there is an optimum blood flow for the heart and, no doubt, in patients this optimum amount will vary with the severity of the disease in the coronary arteries.

The second question concerns venous drainage of blood from the myocardium. When the sinus is ligated blood must escape from the heart by other routes. It seeps through the various channels in the heart and escapes into the four chambers of the heart. In our experimental work on dogs we found that the sinus should be ligated as the first step in the operation. Many sinuses are thin and delicate so that anastomosis in the dog is not possible. After the sinus has been ligated the wall of the sinus becomes somewhat thickened and is more readily manipulated at operation. We found from five to ten days to be the optimum interval between ligation and transplantation.

The third question raised by Dr. Carter concerns arteriovenous fistulae. There are some superficial veins over the right ventricle both anteriorly and posteriorly which can drain blood away from the coronary sinus system and empty the blood into the right auricle. These veins are variable both in dogs and in patients. It is possible for these veins to drain blood away from the myocardial bed producing in effect an arteriovenous fistula. We found such communications in two of our specimens. I have been concerned about this aspect of the problem. I feel that possibly these veins might have to be ligated around the auricle. However, since there is an optimum ceiling that should be placed on inflow into the sinus, these veins may become something of a compensatory mechanism. They cannot keep on enlarging after they reach a certain point because the inflow cannot go beyond the limitation of the graft. This condition is not analogous to congenital arteriovenous fistulae where the development may be progressive. My opinion is that venous communications will not seriously interfere with the circulation. We want to make some long term experiments on this problem.

The fourth question by Dr. Carter concerns myocardial damage in reference to the patient being able to tolerate the operation. I can only say that a patient with coronary artery disease is not a good risk for any operation. Some of our patients have died without operation. Once we get arterial blood into the sinus I think there will be improvement of the heart and that this improvement will, indeed, be significant.

The last part of this discussion concerns thrombosis. We have had about 50 or 60 patent anastomoses. We know when we make a satisfactory anastomosis and when we make an unsatisfactory anastomosis. We know what the factors are for success. The incidence of thrombosis is directly proportional to the amount of operative trauma. I think a solution of this problem is possible.

# THE FACTOR OF RATE OF TRANSFUSION WITH PARTICULAR REFERENCE TO THE INTRA-ARTERIAL ROUTE \*

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A SURGEON'S ABILITY TO CONDUCT a patient safely through the hazards of an operation depends largely on his understanding of pathologic physiology and his ability to act in the light of this knowledge. The increasing frequency and complexity of operations done on the major blood vessels, including operations for portal bed hypertension, coupled with the trend toward more radical procedures for cancer have made a better understanding of hemorrhagic shock and its treatment a matter of great and pressing importance.

A study has been undertaken in which particular emphasis was placed on the route and rate of administration of the blood and fluids used to combat shock.

Although the bone marrow and corpus cavernosum of the penis have been used in emergencies, the intravenous and intra-arterial routes remain the best avenues through which fluids may be introduced rapidly into the vascular bed. Libraries have been written on the matter of intravenous transfusion and the hazards involved and safeguards required in its use.

Relatively little has been written on arterial transfusion although it now appears to be a most useful weapon in combating shock under certain circumstances. In his first contribution to surgery Halstead<sup>4</sup> mentions the use of this route in the treatment of carbon monoxide poisoning but since his work antedated the time when blood transfusions were safe, it was not applied in shock therapy. Except for sporadic mention of the matter, the literature contains no extensive study of arterial transfusion until 1943 when Drs. Kohlstaedt and Page,<sup>5</sup> acting on the suggestion of Col. Sam Seeley, undertook to investigate the possible usefulness of the intra-arterial route. They subjected a series of 40 dogs to prolonged hemorrhagic shock and then replaced 50 per cent of the shed blood. In one half of the dogs the blood was replaced intravenously, and in the other, intra-arterially. Seventy-five per cent of the intra-arterial group survived as compared with 30 per cent of the intravenous group. Using the same degree or stage of shock (measured by the animals' blood pressure response to standard doses of angiotonin), they found that the re-infusion of all the shed blood would result in nearly 100 per cent recovery no matter which route was used. They concluded that when the arterial route was used less blood was needed and that a more prompt and longer lasting elevation of the blood pressure was obtained. In a second group of experiments<sup>6</sup> these same authors found that:

"(1) The delivery of blood into the aorta perfuses the coronary vessels.

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relieving myocardial ischemia, and since myocardial ischemia probably underlies the cardiac dilatation and insufficiency, places the heart rapidly in a state in which it can pump the infused blood to other areas; (2) when, before the infusion, the patient may have been apneic, at its start he will take a deep breath, as if the arterial filling had rapidly extended to the vital medullary centers; (3) in contrast with intravenous transfusion, blood pressure is rapidly restored, and the volume of blood infused is determined, not by time-consuming analyses or by guess, but by the actual capacity of the vascular tree; and (4) a subsidiary advantage lies in the fact that latent bleeding which causes arterial pressure to fall off rapidly is detectable within minutes rather than hours."

Gardiner<sup>2</sup> has described the successful use of arterial transfusion in connection with a technic of deliberately inducing hypotension as an aid in

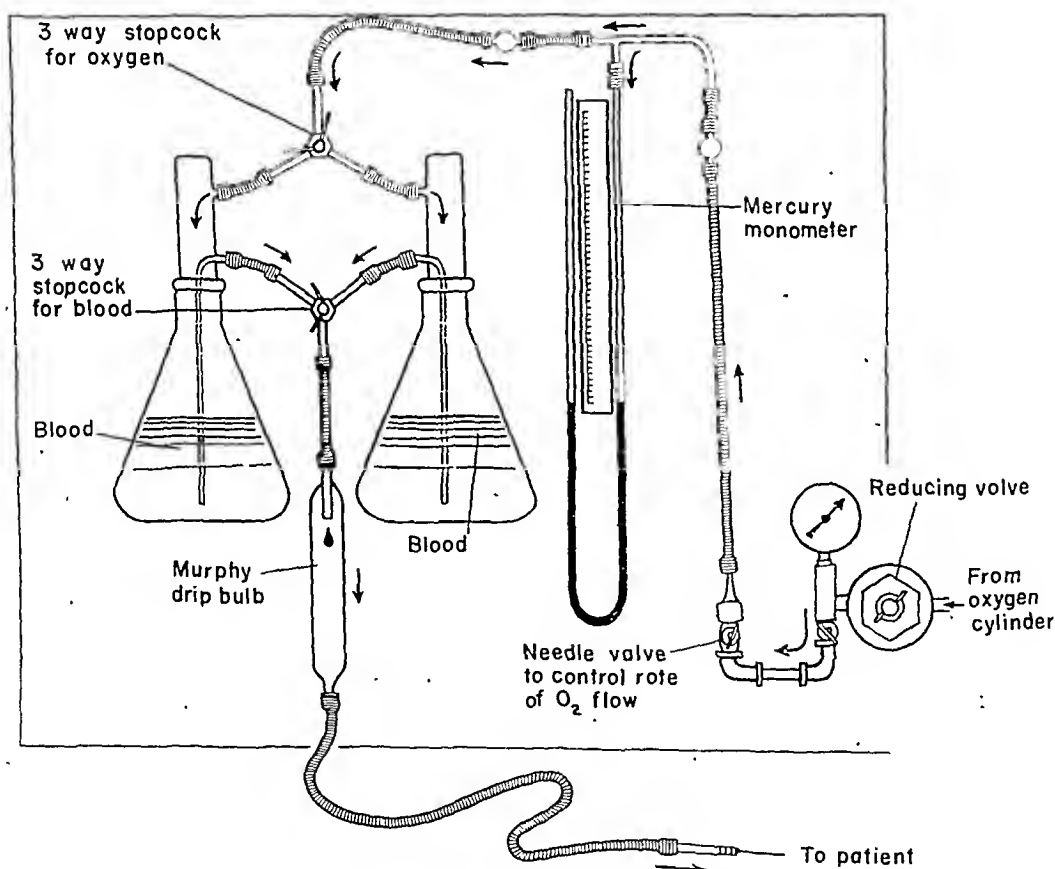


Fig. 1.—Diagram of pressure transfusion apparatus.

hemostasis in the removal of olfactory lobe meningiomas and in the fenestration operation.

At the 77th annual meeting of the Society of Clinical Surgery, Trinchler and Elkin<sup>7</sup> reported preliminary experiments on arterial transfusion. They found that in animals in hemorrhagic shock peripheral blood flow (plethysmograph) was returned to normal levels much more rapidly when the arterial

route was used than when the venous route was employed. This report of Trinchler and Elkin prompted the studies which are described in this paper.

Although our study is primarily clinical, certain animal experiments have been performed in order to gain experience with the technic and to evaluate, if possible, the effect of using the arterial route on the phenomenon of irreversible shock. Details of the experimental studies will appear in a separate

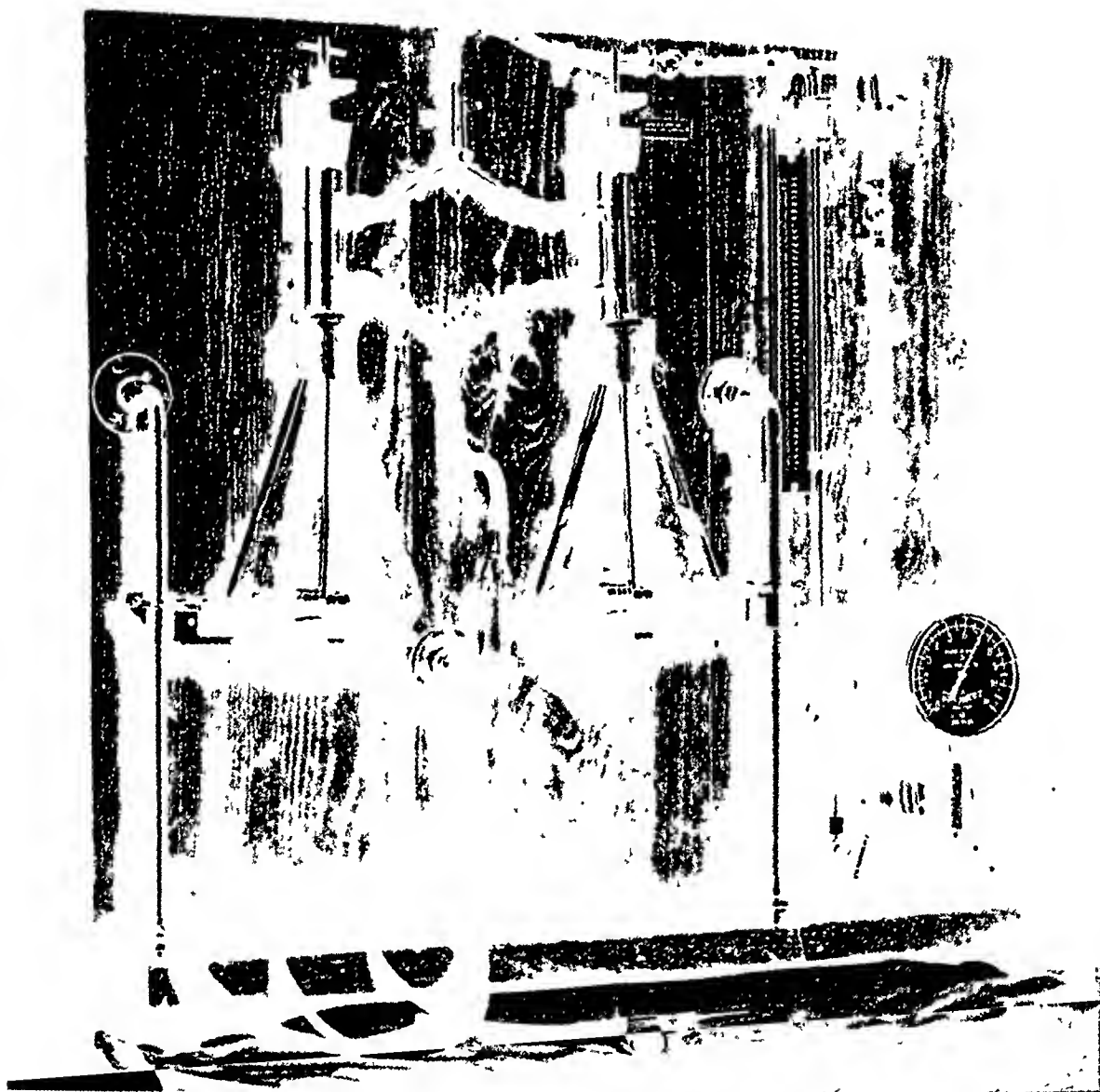


Fig. 2.—Front view of pressure transfusion apparatus.

communication. The lessons learned in these animal studies which have been applied in clinical work are as follows:

(1) Irreversible shock when established according to the criteria set forth by Frank, Seligman and Fine<sup>1</sup> was not favorably influenced by arterial transfusion. Normal blood pressure was restored temporarily, but the animals died of shock within six or eight hours.

(2) The rapid introduction of blood into an artery with the consequent distention of the vessel is a stimulus which often throws the vessel into

spasm. This can be so severe as to interfere markedly with the transfusion. Procaine 1% used locally around the vessel overcomes the spasm. We have supplemented this with stellate ganglion blocks in some of our clinical cases.

(3) Blood pressures more than 20 mm. of mercury higher than the animal's normal could not be obtained although efforts were made to push it higher using very rapid high pressure arterial transfusion. This was apparently due to the animal's own compensatory vasomotor mechanisms.

(4) Congestive heart failure was not encountered in 15 dogs in hemorrhagic shock regardless of the rate of transfusion. This suggests that the cautious gradual increase in the speed of transfusion recommended by Kohl-

staedt and Page may not be desirable in advanced shock states where immediate massive replacement of grossly depleted blood volume is needed. We have not encountered congestive failure in our clinical intra-arterial cases.

#### METHOD

An apparatus has been constructed for introducing fluids under pressure into the veins or the arteries. (Figs. 1, 2, 3.) Blood or other fluid is forced from sterile containers by building up oxygen pressure over its surface. The rate of transfusion is regulated by varying the pressure of the oxygen. A fine needle valve and a mercury manometer permit accurate control. At an oxygen pressure just exceeding the patient's diastolic pressure about one drop of blood will enter the artery during each diastole. Rates up to 500 cc. in three minutes, and faster, can be achieved at oxygen pressures in the range of 250-300 mm. of mercury.

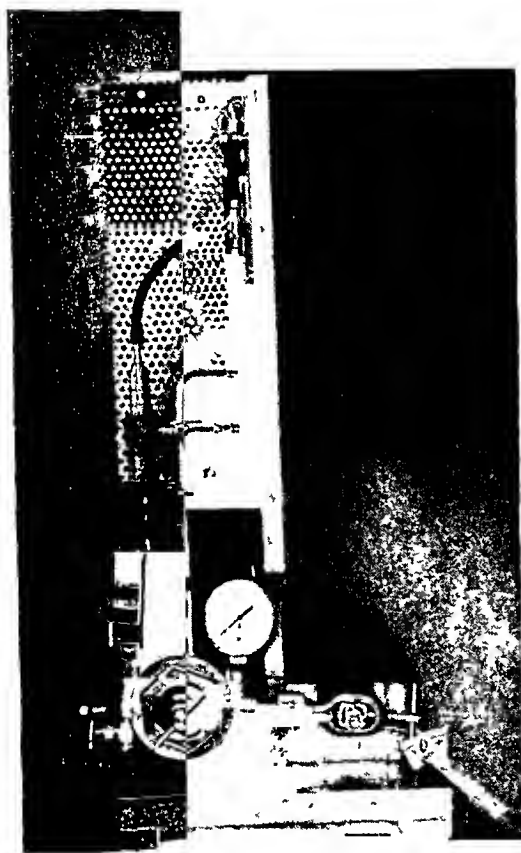


Fig. 3.—End view of transfusion apparatus.

The use of two blood containers connected by three-way valves permits the addition of more blood to the system without interruption of the transfusion. Parts of the machine through which blood passes are easily removed for cleaning and sterilization.

In operating the apparatus care has been taken not to let the blood bottle in use become empty thus allowing air embolism to occur.

The venous pressure machine employed is of the standard type. (Fig. 4.)

*Intravenous Technic.* Although massive intravenous transfusion can be successfully accomplished through multiple needles with gravity flow, it is possible with the pressure apparatus to obtain rapid flow through a single needle. This makes for greater convenience and readily permits adjustment of the rate of flow through a wide range.

A 16-gauge three-part Lindeman needle is placed in a peripheral vein and connected by means of a three-way stopcock with the pressure transfusion machine and the venous pressure apparatus. The latter is used to take frequent

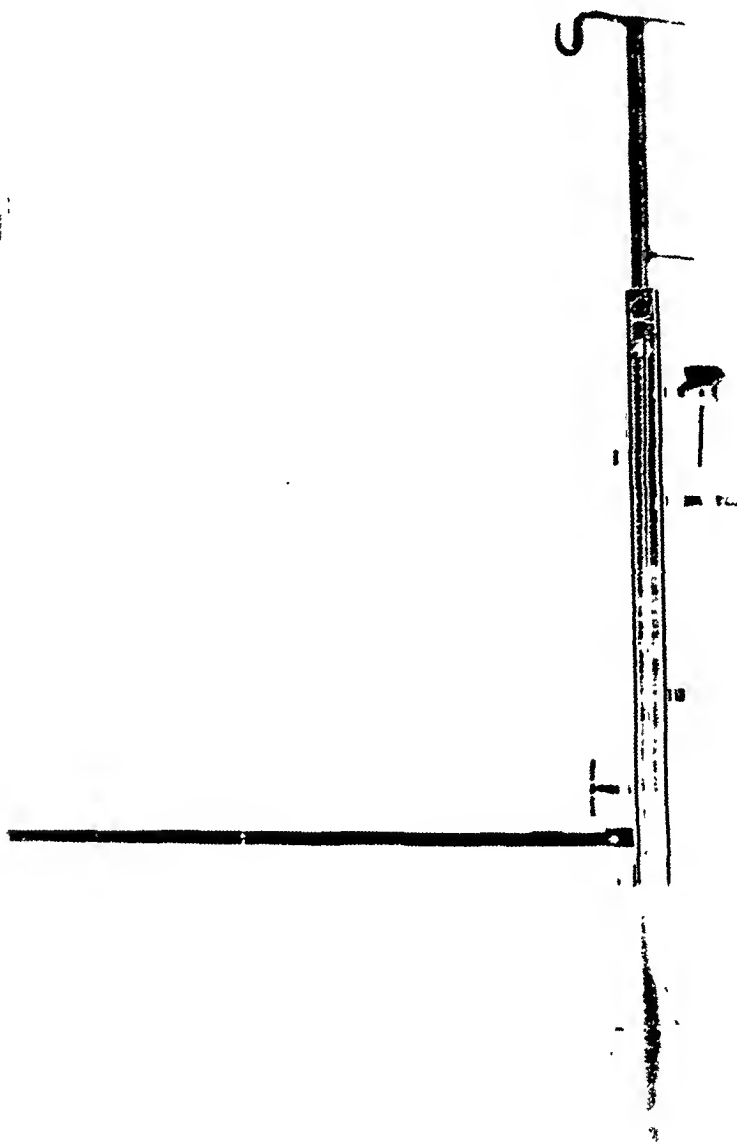


Fig. 4.—Venous pressure apparatus.

venous pressure readings during the period of transfusion. It has not been necessary to tie the needle into the vein.

*Intra-arterial Technic.* Any artery can be used in giving an arterial transfusion. If a major vessel such as the aorta or iliac artery is exposed in the wound, it may be selected; however, it has usually been more convenient to use the radial artery at the wrist. This is exposed through a short trans-



verse incision and delivered from the wound. A 16-gauge Lindeman needle is then introduced centrally under direct vision and does not need to be tied in. This needle is connected directly to the pressure transfusion machine. One per cent procaine is injected locally around the artery to overcome spasm. This is sometimes supplemented by a stellate ganglion block but this is not usually required. Pressures sufficient to cause a slow drip and keep the needle patent are used until rapid transfusion becomes necessary.

Except in dire emergency, blood is the only fluid which we have introduced into the radial artery.

At the completion of the transfusion the needle is withdrawn. If bleeding continues from the puncture site, the vessel is ligated; but this is often unnecessary, if pressure is maintained at the opening for a few minutes.

Venous pressure should be followed in arterial as well as in venous transfusions.

#### CASE REPORTS

**Case 1.** A 57-year-old white woman was admitted with diabetes mellitus, a moderate degree of myocardial damage, and longstanding abdominal echinococcosis. While on the medical ward she had two massive gastro-intestinal hemorrhages. Five transfusions of 500 cc. of blood brought her count up to 4.4 million by the day of operation. At operation great difficulty was encountered in removing an enormous spleen which was adherent to all nearby structures. Splenectomy permitted visualization of the stomach where a large echinococcus cyst was found to have eroded through the lesser curvature of the stomach from the liver, causing the bleeding. A large amount of blood was lost during operation. Shock developed in spite of 500 cc. of blood and 500 cc. of gelatin given intravenously. Arterial transfusion was begun and the pressure returned from 0/0 to 110/70 within fifteen minutes. In that time 500 cc. of blood was given intra-arterially. During the remaining two hours of the operation another 1000 cc. of blood and 500 cc. of gelatin were given intra-arterially. It was found that the systolic blood pressure could be kept at any level between 60 and 100 by varying the rate of flow of the transfusion. The patient left the operating room with a pressure of 100/60 but died 24 hours later. Although systolic pressures of 100 were obtained intermittently during this period, the shock state was never really overcome, perhaps because of severe myocardial disease. No autopsy was obtained.

*Comment.* This was our first clinical case, and in spite of the unfavorable outcome, offered encouragement to proceed with additional trials of arterial transfusion. There is no reason to suppose that the gelatin solution employed in this case played an unfavorable part in the outcome but, for reasons stated below, we prefer not to administer solutions other than blood through the arterial route. In retrospect it would appear that much larger quantities of blood should have been given during the operation as well as during the post-operative period.

**Case 2.** A 15-year-old white girl was admitted with typical signs and symptoms of coarctation of the aorta. Anteoperative blood pressure in the arms was 180/110 but none was obtainable in the legs. Operation: Resection of coarctation with end-to-end anastomosis of the aorta. (See Figure 5 for details of the blood pressure during operation.)

The transfusion was given centrally up the right radial artery. During the early part of the operation the pressure was regulated so that only a few drops entered the patient on each diastole of the heart (A). When the aortic clamps were removed (B) and the

pressure plunged to 0/0, the transfusion was speeded up and 300 cc. of blood was run into the artery in three minutes. As shown in Fig. 5, the pressure rose almost immediately and was thereafter well maintained by the patient. The slow drip of saline intravenously was given so that a patent needle in a vein would be immediately available if the arterial route was not successful.

This patient has had a good result from her operation and no detectable effect from the ligation of her radial artery.

*Comment.* We have since done three other cases of coarctation. In none of them did the need for transfusion develop, and the arterial route was used simply for replacement of the amount of blood lost. In one case in which

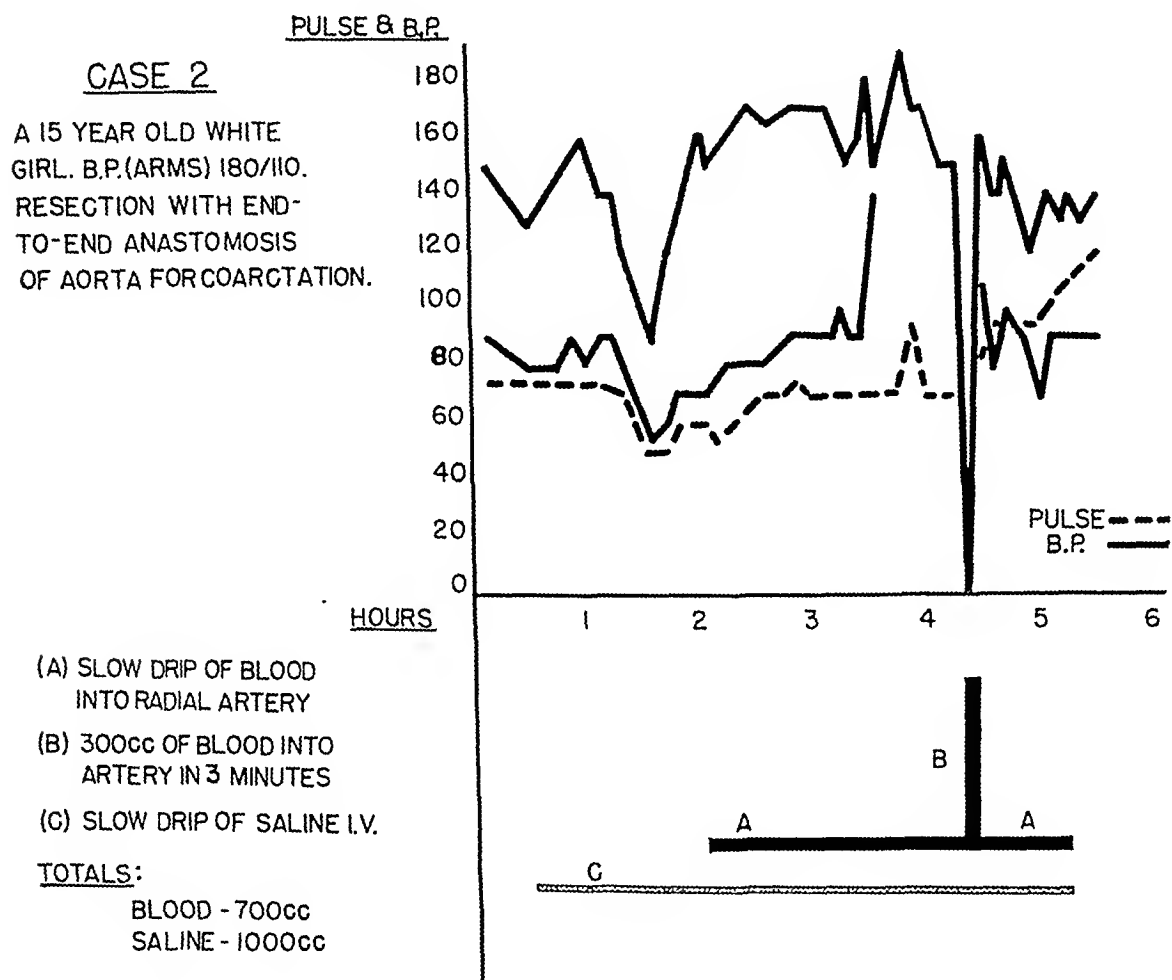


FIG. 5. Case 2.—Arterial transfusion in conjunction with resection and anastomosis for coarctation of the aorta.

massive (600 cc.) hemorrhage occurred from the aortic arch, immediate arterial transfusion prevented any perceptible change in the blood pressure. When the sterile drapes were removed at the end of the procedure in that case, the skin over the radial artery into which the arterial transfusion had been given showed a cyanotic streak 3 to 4 cm. wide and extending from the wrist to the elbow. This disappeared promptly when the arm was adducted and the forearm elevated.

**Case 3.** A 59-year-old woman suddenly developed shock while awaiting elective wiring of a large aneurysm involving the left common iliac artery and the distal portion of the aorta. Emergency celiotomy disclosed considerable abdominal hemorrhage from the

aneurysm, and wiring of the aorta proximal to the aneurysm was performed. Blood was given by arterial transfusion, and gelatin was administered intravenously. Following one particularly massive blood loss, a period of three minutes was required to bring the blood pressure from zero to 105/70 by acceleration of the rate of arterial transfusion. Otherwise the blood pressure was maintained within a safe range in spite of the initial condition of hemorrhagic shock and considerable continuing blood loss. The condition of the patient was good at closure.

*Comment.* It is likely that the same result could have been achieved by use of venous transfusion under pressure.

**Case 4.** A 37-year-old man underwent celiotomy for peritoneal abscess and multiple spontaneous ileo-ileostomies developing secondary to a skip type of regional ileitis. The

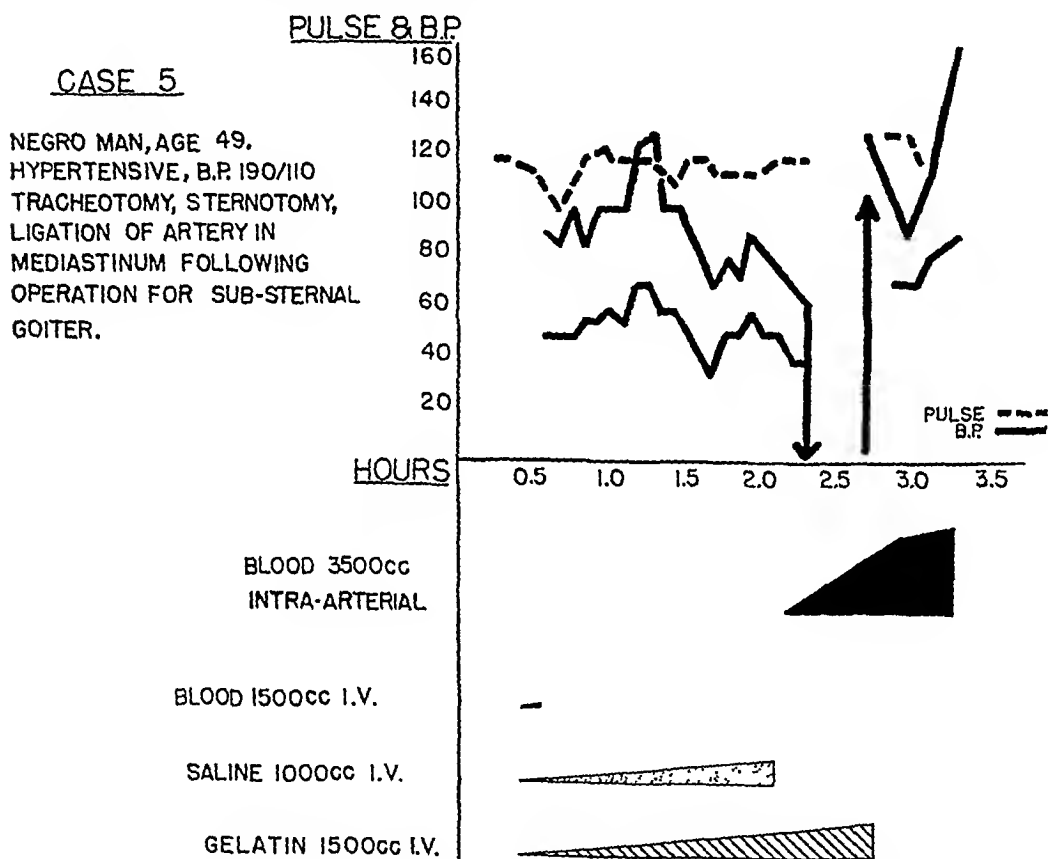


FIG 6. Case 5.—Arterial transfusion for resuscitation following severe post-thyroidectomy hemorrhage.

ileum involved in the ileo-ileostomies was resected and primary anastomosis was performed, leaving approximately three feet of small bowel. Arterial transfusion was begun while the operation was in progress because of severe shock not controlled by venous transfusion. In spite of a long operation and heavy, continuing blood loss, blood pressure was maintained by varying the rate of arterial transfusion. The patient left the operating room in good condition. Total amount of blood administered was 6500 cc., of which 4000 cc. was given intra-arterially, and hematocrit the following day was 42 per cent. Purplish discoloration and vesiculation of the skin over the radial aspect of the forearm receiving the arterial transfusion developed after operation, but did not progress beyond the stage of superficial necrosis.

*Comment.* In view of the extensive unavoidable blood loss which occurred

during the operation, only rapid transfusion could have afforded the necessary support to the patient.

**Case 5.** A 49-year-old hypertensive negro man whose blood pressure normally is 190/110 underwent partial thyroidectomy for a large, substernal, non-toxic, nodular goiter. The operation went well and the gland was removed without splitting the sternum. The patient was returned to the ward in good condition. About an hour later his airway was found to be obstructed and an emergency tracheotomy was done in bed. He was then taken to the operating room where the neck was exposed. Brisk bleeding which could not be controlled by extensive packing with oxidized gauze was seen to be coming from the area beneath the sternum. (See Fig. 6 for details of course in operating room.) When the neck exploration was started, his pressure was 90/50, which was serious hypo-

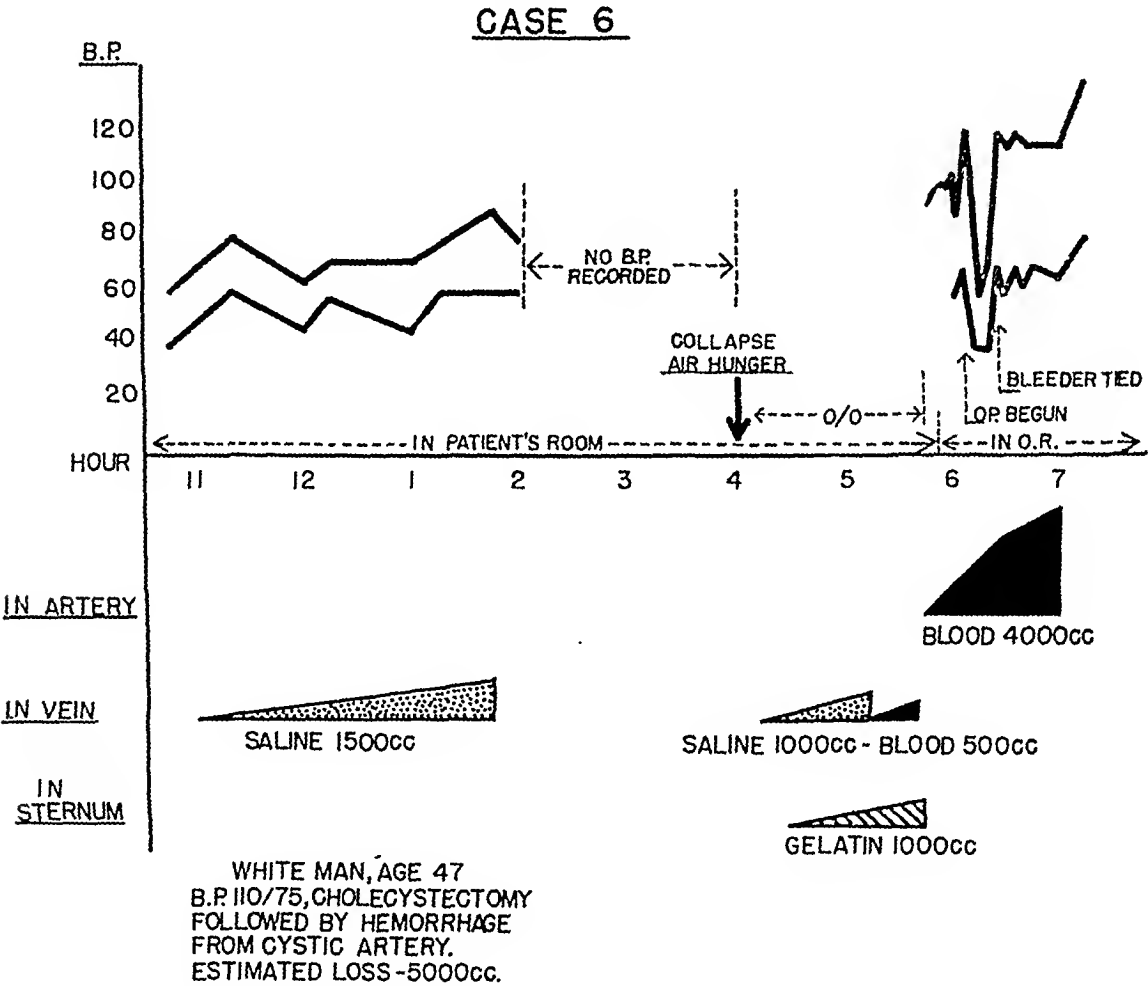


FIG. 7. Case 6.—Arterial transfusion for resuscitation following deep shock resulting from cystic artery hemorrhage.

tension in view of his excessively high normal pressure. During the next one and one half hours 1500 cc. of blood, 1000 cc. of saline and 1500 cc. of gelatin were given intra-venously. In spite of this the blood pressure gradually fell to 60/40 and the pulse stayed in the range of 110 and was of poor quality. At this point it was decided that the sternum would have to be split in order to secure the bleeding point. With the first blow of the mallet on the sternum knife the pressure fell to 0/0. Intra-arterial transfusion was then started at once. About 30 minutes later after 2000 cc. had been given, the pressure was again measured to be 120/70. The bleeding vessel was found to be the left thyro-cervical trunk, which was ligated. Total parenteral therapy of 5000 cc. of blood and 1500 cc. of gelatin. The patient did well postoperatively although his red blood count

showed an anemia of 3.2 million for three days postoperatively. This was corrected by further transfusion

**Case 6.** A white man, age 47, underwent an uneventful cholecystectomy for chronic cholecystitis and cholelithiasis. His normal blood pressure was 110/75. He was returned to his room with a pressure of 60/40 which was thought to be due to a postanesthesia reaction. 1500 cc. of saline was given intravenously and he was watched carefully. At the end of four hours he seemed in good condition, although blood pressure was only 80/50. During the next two hours his blood pressure was not taken. Five and one-half hours postoperatively he suddenly collapsed and was found to have air hunger, unobtainable blood pressure, feeble pulse and a cold sweat. A vein was immediately exposed and 1000 cc. of saline and 500 cc. of blood were pumped in under pressure with a large syringe—at the same time 1000 cc. of gelatin was forced into the sternal bone marrow. In spite of this his pressure remained unobtainable. (See Fig. 7 for details.) An arterial transfusion was begun in the patient's room and it was noticed that more than the usual amount of difficulty was experienced in bringing the blood pressure back to normal. It was not until 1000 cc. of blood had been run in very rapidly (in about eight to ten minutes) that



Fig 8 Case 7.—Showing necrosis in hand.

measurable pressure could be detected, at a level of 90/70. This slow response confirmed our impression that active bleeding was going on since in the absence of such bleeding much less blood should have caused a more prompt rise in pressure. The patient was taken to the operating room with the arterial transfusion running. Anesthesia was induced and the wound opened. When the wound was opened, a marked fall in pressure occurred. Four thousand cubic centimeters of blood were sucked from the peritoneal cavity and many large clots were removed. Estimated blood loss was 5000 cc. The bleeding point could not be located until the intra-arterial transfusion was speeded and the pressure once again forced up into the neighborhood of 110/70. When this was done, the stump of the cystic artery was found to be the bleeding vessel and it was ligated. A total of 4000 cc. of blood was given intra-arterially in about 75 minutes. The patient did well and was discharged from the hospital in good condition.

*Comment.* In this case the intra-arterial transfusion aided in making the diagnosis of continued bleeding. Rapid restitution of blood pressure made possible the discovery of the hidden bleeding artery.

**Case 7.** A 47-year-old woman was subjected to splenorenal vein anastomosis for portal hypertension due to hepatic cirrhosis. Blood loss was approximately 4500 cc.;

# RATE OF TRANSFUSION

5500 cc. of blood was administered by arterial transfusion and 1500 cc. of gelatin by venous infusion during the entire nine and one-half hour procedure. Blood pressure was easily maintained at normal levels, being quickly restored after any sudden drop by acceleration of the arterial transfusion rate. During the nine and one-half hour operation she lay on her right side with the right arm in about 120 degree abduction. The right radial artery received the transfusion centripetally. At the conclusion of the operation when the sterile drapes were removed, the right hand and forearm were cyanotic and cold. These changes were attributed to the unfavorable position of the arm, and it was believed they would prove transitory. The arterial needle was withdrawn and the radial artery ligated. By the fourth postoperative day gangrene involving chiefly the radial portion of the hand was apparent in spite of repeated stellate ganglion blocks (Fig. 8). Death occurred on the sixth postoperative day due to massive esophageal hemorrhage, the splenorenal vein anastomosis being obstructed by thrombus. Postmortem dissection of the arm was not permitted, but arteriograms demonstrated no radial artery shadow in the distal half of the forearm and no radio-ulnar arcade in the hand.

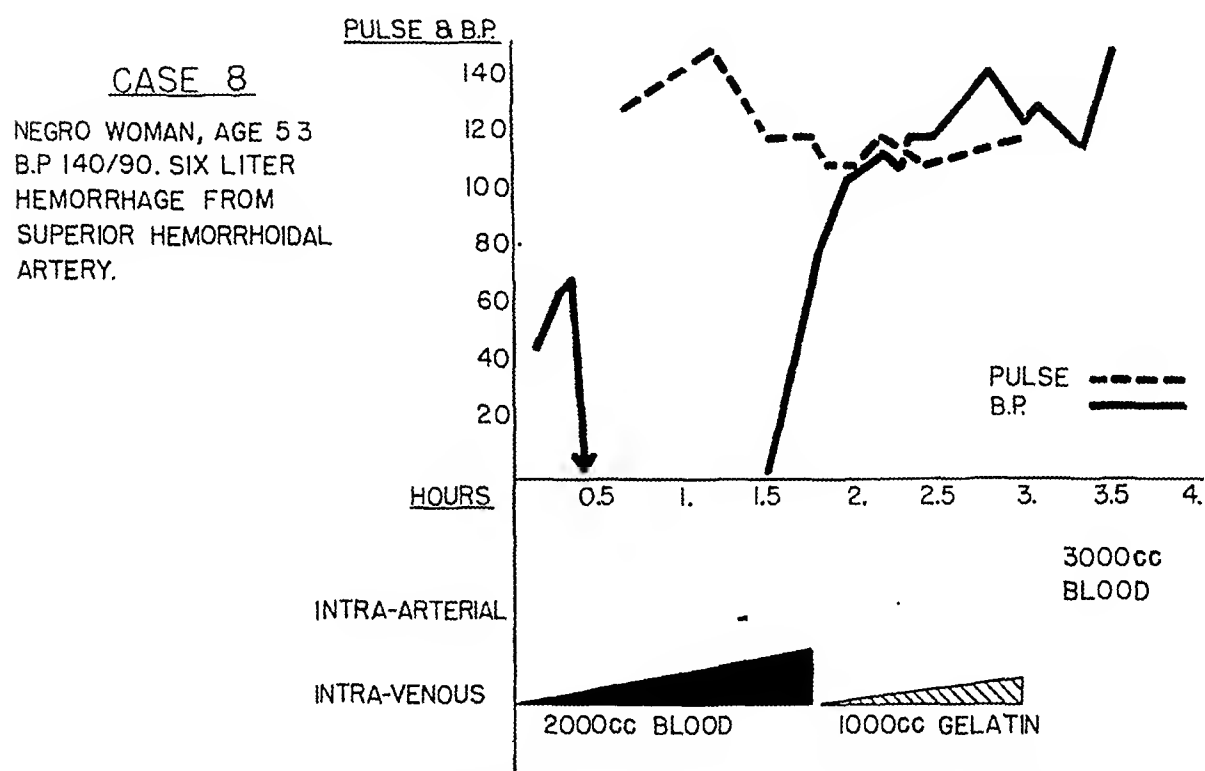


FIG. 9. Case 8.—Rapid intravenous transfusion through multiple needles in conjunction with surgery for massive gastro-intestinal hemorrhage.

*Comment.* Unfortunately, thrombosis, postmortem blood clot, or congenital anomaly could be responsible for the changes in the arteriogram. This complication is difficult to explain because two possible contributing factors exist: (1) Impaired venous return from that arm due to poor position may have resulted in axillary vein thrombosis. (2) The radial artery was ligated at the wrist and the normal radio-ulnar anastomosis of the hand may not have been present. This is the only instance of this type which we have encountered.

**Case 8.** Eighteen days after abdominoperineal rectal resection for carcinoma a 53-year-old woman suddenly showed signs of massive intra-abdominal hemorrhage. For about 30 minutes neither blood pressure nor peripheral pulse could be detected, in spite of about 1500 cc. of blood transfused by venous route over a period of one and three-quarters hours. After 2000 cc. of blood had been administered by the centripetal arterial route

in 20 minutes, the systolic blood pressure had reached 100 mm. of mercury (Fig. 9). The superior hemorrhoidal artery could then be recognized as the source of the bleeding, and it was ligated. The patient left the operating room in good circulatory condition. Total blood loss was 6000 cc. and hematocrit 18 hours later was 41.2 per cent. Postoperatively the skin of the forearm over the radial artery used for the transfusion developed purplish discoloration and marked vesiculation. Although the hemorrhagic shock was controlled adequately, death occurred on the eighth day from peritonitis and lower nephron nephrosis.

*Comment.* The need to administer Group O blood which had not been cross-matched may have played a part in causing the renal lesion, but other signs of transfusion reaction were not found. The changes of the forearm did not show signs of progressing beyond superficial necrosis during the period of survival.

**Case 9.** A 66-year-old white man was admitted to the hospital with massive gastrointestinal hemorrhage from a benign gastric ulcer. 3500 cc. of blood was given anterooperatively following which it was decided that emergency gastrectomy must be done because of great difficulty in maintaining adequate blood pressures.

During operation it was necessary to give another 3000 cc. of blood to replace blood lost by hemorrhage and prevent shock. This was done through three large intravenous needles. Venous pressures were taken frequently during the procedure. On one occasion the venous pressure rose to 155 mm. of water and because of this the transfusions were all retarded to slow drips. The venous pressure fell to 50 and transfusions were speeded again to compensate for bleeding in operative field. This type of management was carried out through the operation. The patient did well and his red blood count the next day was 3.2 million.

*Comment.* By carefully following venous pressure readings we were able to transfuse 6500 cc. of blood into a 66-year-old man in a relatively short period of time without causing congestive heart failure. Possible citrate intoxication was combatted by calcium gluconate administration.

#### DISCUSSION

1. The choice of route of transfusion is unlikely to influence the course of *irreversible* shock, even provided adequate quantities are given. The recovery of animals from otherwise irreversible shock has been accomplished by Frank et al<sup>1</sup> by cross-perfusion of the liver with oxygenated blood from a donor animal. Their studies indicated that administration of blood and fluids by the portal system may be more effective in treatment of shock than when the peripheral veins are used. We have not yet investigated this aspect of the problem. However, in shock which has not reached a stage of irreversibility, the arterial route appears to make the effects of transfusion available more rapidly to the organism. An added benefit is the direct hydraulic effect of raising the pressure in the aortic arch which will immediately be reflected by increased blood flow in the cerebral, coronary, hepatic, and renal vessels.

2. The rate of replacement of massive blood loss deserves increased emphasis. The amount of blood required for replacement after hemorrhage is underestimated many times (Case 5) as indicated by anemia in the immediate post-treatment period. A frequent error is too rapid introduction of blood by the venous route. This hazard is best avoided by frequent determinations

of venus pressure during the transfusion period. This is especially important to the patient with diminished cardiac reserve. The latter is the often encountered situation when the surgeon finds himself trying to balance the patient on the narrow line between congestive heart failure on the one hand and shock on the other.

3. The fluid changes incident to the treatment of shock impose a heavy strain on the cardiovascular system. If cardiac reserve is not adequate, heart failure may supervene. When time permits preoperative cardiovascular evaluation, such diminished reserve may be discovered and prophylactic digitalization instituted. The importance of this aspect of the problem is supported by recent work of Glasser and Page<sup>8</sup> who transfused dogs after hemorrhagic shock. Of a group given a good prognosis those receiving ouabain showed 71 per cent survival, those not receiving it only 5 per cent survival.

4. With respect to the nutrition of the tissues of the hand and forearm incident to arterial transfusion, two factors are important:

a) Ligation of the radial artery may result in necrosis of a part of the hand in those rare cases where the palmar anastomoses between radial and ulnar arteries are incomplete. Such anomalies are uncommon, however, and this small risk is to be accepted as part of a life-saving arterial transfusion. If time permits, these cases may be discovered by externally compressing the radial artery before operation and observing the effect on the hand. In some adults ligation of the radial artery probably will be necessary.

b) For the arterial route only blood should be used, since it is believed the dilution of brachial arterial blood by plasma, gelatin, or saline increases the risk of ischemic necrosis of the tissues of the forearm and hand. Kohlstaedt and Page administered plasma to three patients via the radial artery. In two of these patients an area of sloughing appeared on the flexor surface of the forearm which had been used for the transfusion.

In our experience four patients receiving blood centripetally in the radial artery showed marked purplish discoloration and coolness of the skin overlying the radial artery in the forearm and in two of these blistering of the skin occurred; in the other two the changes disappeared rapidly. It is believed these changes are due to varying degrees of vasospasm of the primary branches of the radial artery due to the introduction of large volumes of cold blood under high pressure into that vessel. Damage to vasa vasorum and small branches from the high pressures employed may have been a factor.

5. It is important to emphasize that when shock is anticipated more than enough blood should be held in readiness before operation. On occasion as much as 5000 cc. of blood have been cross-matched for a single patient.

6. In resection of the coarcted segment of aorta with primary anastomosis marked hypotension sometimes develops when the aortic clamps are removed after completion of the anastomosis. Peripheral resistance is decreased because the heart has not only a well developed collateral bed but also a normal aortic channel into which to empty. Blood pressure falls sharply until



vasomotor mechanisms make the adjustment, or death supervenes. Artificial hydraulic support of aortic arch pressure appears to be the physiologic antidote to this hypotension. Such a solution is provided by centripetal arterial transfusion.

It is true in most instances that this measure of protection may not be necessary. Nevertheless, one patient operated upon in this hospital died suddenly immediately after removal of the aortic occluding clamps. This occurred before the development of the pressure transfusion apparatus.

#### SUMMARY

A review of pertinent literature indicates certain advantages of the arterial over the venous route of blood transfusion in the treatment of shock. However, it is possible that some of the benefits attributed to arterial transfusion are actually due to the rapid rate at which the blood had been administered.

An apparatus is described which makes possible prolonged, controlled, rapid administration of fluids through vein or artery. Frequent determination of the venous pressure is essential to avoid development of pulmonary edema during rapid transfusion. In eight cases of severe shock the blood was administered arterially by use of the apparatus described. Recovery occurred in each instance. The relative importance of the route of transfusion on the one hand and the rate of administration on the other is difficult to evaluate. It is possible that an advanced stage of shock may develop on occasion which is irreversible to venous transfusion but reversible if the arterial route is employed. The studies here reported do not answer this question.

During operative procedures characterized by excessive blood loss, and therefore requiring large replacement volume, the ability to control blood pressure through a hydraulic system attached to the arterial circulation is an additional safeguard against shock and a great comfort to the surgeon.

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DISCUSSION.—DR. DANIEL C. ELKIN, Emory University, Ga.: The clinical results of intra-arterial transfusion have closely paralleled the observations which we have

made on laboratory animals. Blood flow to an extremity was selected as a criterion for determining changes to the peripheral blood flow, on the premise that since this flow is restored late in the correction of hemorrhagic shock, flow to vital centers probably had already been restored. In the anesthetized dog, blood flow to a hind limb was measured by use of an air plethysmograph, and recorded optically. The opposite femoral artery was cannulated for controlled hemorrhage, optically recorded blood pressure measurements, and the re-infusion of blood. After a basal period of 30 minutes, normal blood pressures and flows were recorded. The animals were then bled rapidly until the mean arterial pressure reached 50 mm. of mercury. Hemorrhagic hypotension was maintained at this level by repeated small hemorrhages for intervals varying from 30-75 minutes. At the end of this interval, all the blood removed was re-infused, in one group of animals by the intra-arterial route, in the other by the intravenous route. In the intra-arterial group, the blood was re-infused at a pressure approximately 50 mm. of mercury greater than the mean blood pressure and at a rate of approximately 100 cc. per minute. Pressure and flow determinations were made throughout the infusion period and at varying intervals thereafter up to one hour.

The intravenous transfusions were allowed to flow by gravity at a rate substantially greater than that used in the routine clinical administration of blood, and which was considered to approach the maximum pressure permissible to avoid right heart congestion. The rate averaged 25 cc. per minute. When an intra-arterial transfusion was initiated at a pressure approximately 50 mm. of mercury greater than the animal's mean arterial pressure, there was almost instantaneous rise in pressure throughout the arterial system, as noted by recording the pressure in arteries at some distance from the site of transfusion. These flows reached the normal values at an average of about seven minutes, some as quickly as four minutes. Upon discontinuing the intra-arterial transfusion, the arterial pressure and blood flows were maintained indefinitely and recovery ensued in all instances. Following intravenous transfusion, recovery was considerably slower, requiring a period of approximately four times longer. There was also a tendency for blood pressure and flow to be maintained at a lower level than normal after the transfusion was completed.

From our clinical experience, it appears that intra-arterial transfusion has a definite place in the treatment of severe traumatic shock, exsanguination in obstetric emergencies, and intra-abdominal and intrathoracic hemorrhage.

DR. GEORGE H. HUMPHREYS, New York: I would like to acknowledge our indebtedness to Dr. Elkin and Dr. Pilcher for their work, without knowledge of which we would not have undertaken to treat these patients. I can say from experience, especially with coarctation cases, that it is a matter of great reassurance to a physician that he can replace blood rapidly, and I can say that in many cases a fall in pressure could be fatal. It is necessary to have a well-organized blood bank to produce blood rapidly. It should be used only in cases of great emergency.

DR. HILGER P. JENKINS, Chicago: Following the dictum that we should strive to carry out the procedure which will do the most good and the least harm, I would like to suggest that a cuff or a patch of gelatin sponge (gelfoam) be used to control hemorrhage from the arterial puncture wound and thus obviate the necessity and hazards of ligation of the vessel.

This suggestion is based on recent experimental work on dogs, in which it was possible in most instances to obtain control of hemorrhage and restoration of blood flow after a scalpel wound of the coronary artery by the gelatin sponge patch technic.

DR. CLARENCE CRAFOORD, Stockholm, Sweden: There has been some talk about the rapid fall of blood pressure caused by rapid release of the aortic clamps. This is

difficult for me to understand. I have had the aorta cross-clamped in 70 cases of coarctation and patent ductus, and have never taken any precaution to release them slowly, and have no blood pressure fall of significance in connection with removal of the clamps. In cases of patent ductus where there is no collateral circulation, when aortic clamps are applied the blood pressure rises sometimes to 200 mm. of mercury or more, and has dropped to the previous level after the clamps have been released. I do not think the explanation given by Gross is the correct one, that is, that it is the releasing of the clamps that causes the fall in blood pressure. I am convinced that there is some other factor such as unsatisfactory ventilation during the anesthesia for, so far as I know, all these patients are allowed to breathe themselves, and have not been under controlled respiration during the operation. I believe that if adequate ventilation were used, the small additional stress to which the heart is subjected on removal of the aortic clamps would not have affected the heart.

There is a point I would like to stress in connection with giving large amounts of blood rapidly. I believe it better to give fresh blood from heparinized donors, rather than to give old blood. Fresh blood will function much longer than stored blood from a blood bank. ..

DR. E. I. EVANS, Richmond, Va.: I wish to compliment Dr. Porter highly for this splendid presentation, and not the least for the dramatic effect. After wars are ended we are apt to think we have learned all there is to know about traumatic and surgical shock. In going over recently the work of Cleghorn and Shute from Canada, it is evident to me that a tremendous amount is still to be learned.

For those who still worry about the introduction of whole blood as "foreign material" into the blood stream, we may be reminded of what John Hunter said to his students, "Blood is that out of which all living cells are made and from which they are supported."

DR. RALPH F. BOWERS, Memphis, Tenn.: I am very much interested in the new agents and technics employed in replacement therapy. Intra-arterial transfusion has a place which will prove of inestimable value in some cases. My associations have been with surgeons who stressed careful hemostasis and gentle handling of tissues and, therefore, utilized replacement therapy as an adjunct, when it was not possible to prevent the loss of blood. There is developing a philosophy in surgeons today, the older ones as well as the younger ones, which reflects the sense of false security so far as blood loss is concerned, because we can have a bottle of blood hanging on a pole by the patient's side, which allows us to "lose all the blood we wish" and still save the patient. The blood in the bottle is not as good as the patient's own blood. The recent emphasis placed upon replacement therapy has brought about great improvement of technics and agents. Therefore, great emphasis has been exercised about replacement in the past decade. Instead of applying the emphasis on replacement, we should return to emphasizing the time-honored fundamental principle of hemostasis and vigorously apply thought and energy to the prevention of the loss of the patient's blood during the operation.

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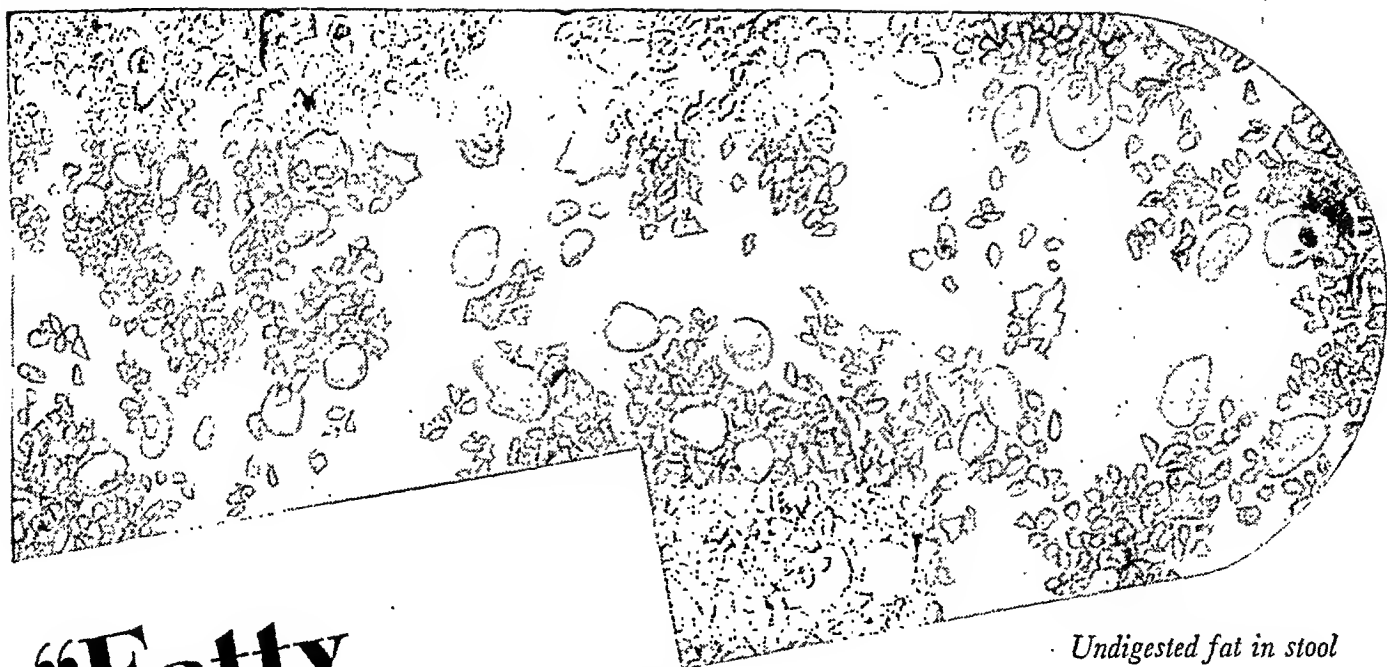
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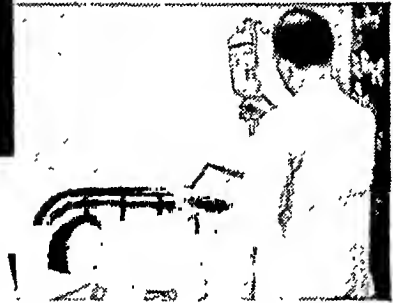
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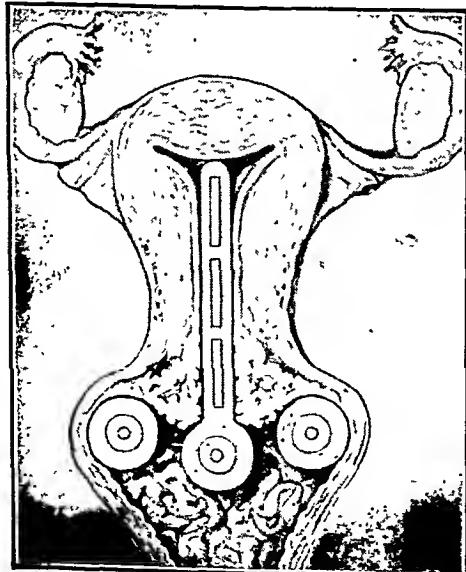
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## OBSERVATIONS ON VISCERAL PAIN\*

### (1) VISCERAL TENDERNESS

F. H. BENTLEY, O.B.E., M.D., F.R.C.S. (Eng.)

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THE MANY AND DIVERSE VIEWS that have been held on the subject of visceral sensation are due chiefly to differences of observation, which lead naturally to differences in interpretation. So long as the basic clinical and experimental findings remain in dispute there can be no agreement about the sensory mechanisms involved in visceral pain. The actual situation of the deep tenderness that occurs in abdominal disease; the presence and distribution of skin hyperesthesia in visceral disorders; the effect of procaine when injected into the area of pain-reference: these are all examples of conditions in which directly opposing observations have been made.

It is necessary at the present time to re-examine some of the facts of visceral sensation and to report simply the findings. In this paper are described experiments on the location of deep tenderness found in patients suffering from chronic peptic ulcer. By tenderness is meant that a sensation of pain is evoked when the area is pressed upon. The questions that the experiments were designed to answer are:

In patients suffering from chronic peptic ulcer,

(I) Is the ulcerated wall of the stomach or duodenum itself tender (as claimed by Kinsella and Palmer)?

or

(II) is the pain that is produced by pressure in the epigastrium invariably due to irritation of the sensitive anterior parietal peritoneum by the ulcerated viscus (as suggested by Morley and Twining)?

or

(III) does the pain arise from pressure on hyperesthetic areas in the anterior abdominal wall caused by a viscerosensory radiation from the ulcerated area of the stomach or duodenum (the classical Mackenzie view)?

(I) EPIGASTRIC TENDERNESS IN PATIENTS WITH CHRONIC PEPTIC ULCER WAS ABOLISHED WHEN THE SPLANCHNIC NERVES WERE BLOCKED WITH PROCAINE  
TECHNIC OF SPLANCHNIC BLOCK

No sedative was given. The abdomen was examined and then, with the patient in the sitting position, 25 ml. of 1 per cent procaine were injected about

\* Submitted for publication, April, 1948.

the anterolateral aspect of the body of the first lumbar vertebra on each side. The injection was accepted as satisfactory only when there was faintness and a fall of blood pressure. The patient was laid down again, and the abdomen re-examined. Evidence of skin anesthesia was looked for, lest the 12th intercostal or the 1st lumbar nerves should have been blocked. Anesthesia was not found in any case.

In the first two patients reported below, 50 ml. of 1 per cent procaine were injected into the muscles of the lumbar region before splanchnic block was attempted. This injection resulted in no alteration in the epigastric tenderness. It was not thought necessary to carry out further controls on the effect of this amount of procaine on pain sensitivity.

#### CASE REPORTS

**Case 1.**—C. P. Male. Age 54. History of 17 years ulcer pain. A large pyloric ulcer was demonstrated radiologically. Examined during an acute exacerbation. Patient ill and frail.

*Examination:* (a) No hyperesthesia of the skin of the epigastrium; (b) marked tenderness on moderate pressure in the epigastrium. Tenderness diffuse, but maximal at one place (x, Fig. 1).

#### SPLANCHNIC BLOCK

*Re-Examination:* All tenderness gone. Now possible to palpate deeply in the upper abdomen with no trace of discomfort.

*At operation* one week later, a large ulcer of the pylorus and first part of the duodenum was found.

**Case 2.**—G. C. Male. Age 45. History of 5 years ulcer pain. Duodenal ulcer demonstrated radiologically. Examined during an acute exacerbation.

*Examination:* (a) No hyperesthesia of the skin of the epigastrium; (b) Marked tenderness on moderate pressure high up in the epigastrium. Tenderness well localized to one place (x, Fig. 2).

#### SPLANCHNIC BLOCK

*Re-Examination:* All tenderness gone. Now possible to palpate deeply in the upper abdomen with no trace of discomfort.

*At Operation* 9 days later, a large ulcer of the anterior wall of the first part of the duodenum was found.

**Case 3.**—B. D. Female. Age 50. History of 10 years ulcer pain. Duodenal ulcer demonstrated radiologically.

*Examination:* (a) No hyperesthesia of the skin of the epigastrium; (b) Deep tenderness in the right epigastrium, well localized to one place (x, Fig. 3).

#### SPLANCHNIC BLOCK

*Re-Examination:* All tenderness gone. Now possible to palpate deeply in the upper abdomen with no trace of discomfort.

*At Operation* 5 days later, an ulcer involving the anterior wall of the first part of the duodenum was found.

**Case 4.**—R. M. Male. Age 40. History of 7 years ulcer pain. Duodenal ulcer demonstrated radiologically. Examined at the end of an acute exacerbation.

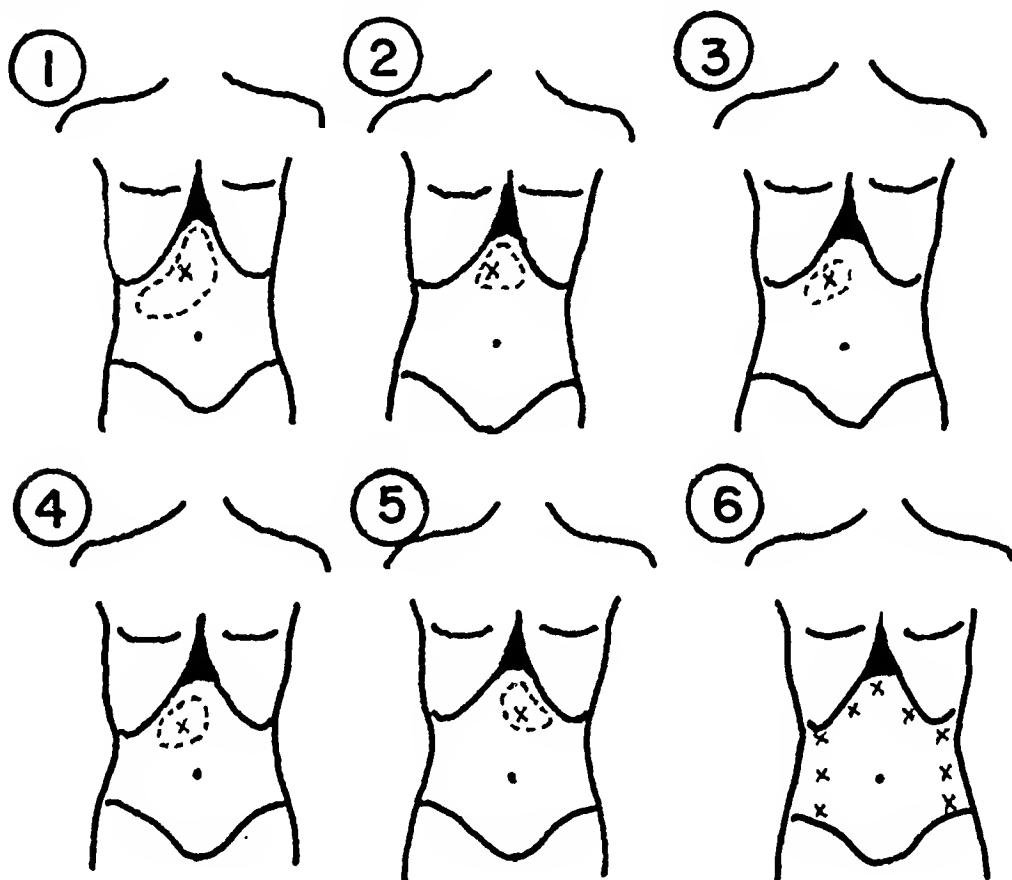
*Examination:* (a) No hyperesthesia of the skin of the epigastrium. (b) Deep tenderness in the right epigastrium, well localized to one place (x, Fig. 4).

#### SPLANCHNIC BLOCK

*Re-Examination:* All tenderness gone. Now possible to palpate deeply in the upper abdomen with no trace of discomfort.

Patient not brought to operation.

**Case 5.**—J. G. P. Male. Age 40. History of 10 years ulcer pain. Gastric ulcer demonstrated radiologically. Examined in an acute exacerbation.



FIGS. 1-5.—Site of maximal tenderness in each case. (Cases 1-5.)

FIG. 6.—Sites of injection of procaine to produce abdominal wall block.

*Examination:* (a) No hyperesthesia of the skin of the epigastrium; (b) Marked tenderness on moderate pressure in the left epigastrium. Maximal at one place (x, Fig. 5).

#### SPLANCHNIC BLOCK

*Re-Examination:* All tenderness gone. Now possible to palpate deeply in the upper abdomen with no trace of discomfort.

*At Operation* 4 days later, an ulcer of the lesser curve of the stomach was found, forming a mass about  $\frac{3}{4}$ " in diameter, free from adhesions in front and behind.

#### CONCLUSIONS

Epigastric tenderness occurring in patients suffering from chronic peptic ulcer was abolished when the splanchnic nerves were anesthetised. The peritoneal nerve supply was still intact; the tenderness could not have been due, therefore, to irritation of the anterior parietal peritoneum by the ulcerated

viscus. The results indicated either that the ulcerated area was itself the site of the deep tenderness; or that the tenderness was due to pressure on hypersensitive areas in the abdominal wall, for the afferent limb of any viscerosensory radiation would have been abolished by the splanchnic block.

In order to investigate the pain sensitivity of the ulcerated viscus it was necessary to stimulate the ulcer area directly, and not through the sensitive anterior body wall.

## (II) THE WALL OF THE STOMACH OR DUODENUM INVOLVED IN AN ULCER WAS SENSITIVE TO DIRECT MECHANICAL STIMULATION

Operation was performed under abdominal wall block on patients suffering from chronic peptic ulcer and in whom epigastric tenderness had been an obvious clinical feature. The anesthetic was introduced by subcostal injection and into the rectus sheath (Fig. 6). A total of 150 ml. of 1 per cent procaine, containing a concentration of 1 in 100,000 adrenaline hydrochloride, was employed. As the observations were on the persistence and not on the abolition of pain, controls were not needed.

The patients were given  $\frac{1}{6}$  gr. morphia or of "Omnopon" as a sedative. This did not affect the precision of the pain responses, although they became unreliable if heavier sedation was employed. The abdomen was opened through a right upper paramedian incision.

There are many difficulties in making direct observations on visceral sensation in the conscious individual. The patient needs to be fully responsive to unpleasant stimuli, and yet should lie tranquil and calm in order that the response to any stimulation of the viscus may be precise and significant. If the patient is in discomfort it is impossible to rely on his appreciation of a new pain. In addition, observations have to be carried out with much gentleness, and the stimulus applied to the desired area without causing any interference with other tissues, as, for example, by deforming or pulling on the lesser omentum.

These conditions are not easy to fulfill, and only when they were met was the experiment accepted. In some patients it was possible to make simple observations. In others, of more phlegmatic mould, the observations could be extended.

**Case 6.**—J. D. Male. Age 40. Gastric ulcer. Preoperative tenderness in left epigastrium.

*Operation:* Gentle retraction of the left half of the wound revealed an ulcer at the centre of the lesser curve, forming a mass in the stomach wall about  $\frac{3}{4}$  inch in diameter. The ulcer mass extended slightly into the lesser omentum. It was free from adhesions in front and behind.

*Tests.* (a) Ulcer mass gently pressed with finger—*continuous pain while pressure maintained*; (b) Insertion of a fine hypodermic needle into the mass—*immediate pain as needle introduced*; (c) Injection of 0.5 ml. 6 per cent NaCl into the mass—*pain, lasting several minutes*.

All these tests were performed away from the lesser omentum in that part of the mass in the anterior stomach wall.

(d) Similar tests to (a) (b) and (c) were carried out at a normal part of the lesser curve—no sensation.

General anesthetic given. Partial gastrectomy performed.

**Case 7.**—B. D. Female. Age 50. Duodenal ulcer. Preoperative tenderness in the right epigastrium.

*Operation:* Scarred first part of duodenum with ulcer mass  $\frac{3}{4}$  inch in diameter adherent to the pancreas behind, but free from adhesions in front.

*Tests:* (a) Anterior surface of the mass gently rubbed with finger—*continuous pain*; (b) Anterior surface of the mass gently pressed with the finger—*continuous pain*.

General anesthetic given. Partial gastrectomy performed.

**Case 8.**—E. K. R. Female. Age 59. Gastric ulcer. Preoperative tenderness in the left epigastrium.

*Operation:* Gentle retraction of the left half of the wound revealed an ulcer at the lower part of the lesser curve, forming a mass in the stomach wall about 1 inch in diameter, not extending into the lesser omentum. It was free from adhesions in front and behind.

*Tests:* (a) Ulcer mass gently rubbed with finger—*continuous pain*; (b) Ulcer mass gently pressed with finger—*continuous pain*; (c) Abdominal wall depressed against ulcer mass—*pain (as preoperatively)*; (d) Anterior parietal peritoneum, where it was seen to impinge against the ulcer, rubbed with the finger—*no sensation (confirming the abdominal wall anesthesia)*; (e) Left hand introduced between the stomach and the anterior abdominal wall, and the abdominal wall pressed against the hand—*no sensation*; (f) Hand removed and abdominal wall pressed against the ulcer mass—*pain as before*; (g) Needle inserted into the ulcer mass—*immediate pain as needle introduced*; (h) Injection of 0.5 ml. 6 per cent NaCl into the mass—*pain, lasting several minutes*; (i) Pressure on the stomach, rubbing with the finger, insertion of needle and injection of 6 per cent NaCl at a normal part of the lesser curve—*no sensation*.

General anesthetic given. Partial gastrectomy performed.

**Case 9.**—J. P. Male. Age 37. Duodenal ulcer. Preoperative tenderness in the right epigastrium.

*Operation:* Ulcer mass  $1\frac{1}{2}$  inches in diameter occupying the first part of the duodenum and adherent to the pancreas, but free from adhesions in front.

*Tests:* (a) Anterior surface of the mass gently rubbed with finger—*continuous pain*; (b) Injection of 0.5 ml. 6 per cent NaCl into the mass in the anterior wall of the duodenum—*pain, lasting several minutes*; (c) Injection repeated at normal point on the lesser curve—*no sensation*.

General anesthetic given. Partial gastrectomy performed.

**Case 10.**—G. W. E. Male. Age 48. Gastric ulcer. Preoperative tenderness in the centre of the epigastrium.

*Operation:* Ulcer at the centre of the lesser curve, forming a mass 1 inch in diameter. The lesser omentum was drawn into the edge of the lump, but no extension of the mass into the omentum. Mass free from adhesions in front and behind.

*Tests:* (a) Anterior surface of the mass gently rubbed with finger—*continuous pain*; (b) Insertion of a fine hypodermic needle into the anterior aspect of the mass—*patient instantly said "Oh! you're sticking a needle in me!" This point was  $\frac{1}{2}$  inch from the lesser curve border of the stomach, and the needle entered about  $\frac{1}{4}$  inch in depth*; (c) Injection of 0.5 ml. 6 per cent NaCl into the mass—*pain, lasting several minutes*; (d) Pressure on the stomach, rubbing with the finger, insertion of a needle and injection of 6 per cent NaCl at a normal point of the lesser curve—*no sensation*.

General anesthetic given. Partial gastrectomy performed.

## CONCLUSION

Direct stimulation of the exposed viscus showed that the stomach or duodenal wall involved in an ulcer was sensitive to pressure, to needle prick, and to chemical stimulation. This pain sensitivity of the viscus could not be due to pressure on hypersensitive nerves in the body wall or to irritation of the anterior parietal peritoneum. The ulcerated viscus itself was sensitive to mechanical and chemical stimulation.

## DISCUSSION

There are two afferent pathways from the upper abdomen. One by the splanchnic nerves, the other by the nerves of the abdominal wall.

When the splanchnic nerves were blocked and the abdominal wall nerves were intact, the epigastric tenderness associated with a peptic ulcer was found to be abolished.

When the abdominal wall nerves were blocked, but the splanchnic nerves were intact, the exposed ulcerated area of the stomach or duodenum was found to be sensitive to pressure, to pin prick, and to chemical stimulation. The non-ulcerated part of the lesser curve of the stomach was not sensitive to these stimuli.

It is possible, therefore, to conclude that abdominal tenderness associated with a peptic ulcer is produced by pressure on the ulcerated wall of the stomach or duodenum. *That is, pain arises directly from the viscus.* The afferent pathway is by the splanchnic nerves. This observation is in agreement with the recent findings of Ray and Neill, who have confirmed by valuable studies in sympathectomised patients that pain sensitivity from the stomach is mediated wholly by afferents running with the visceral nerves.

This conclusion does not, of course, deny that if the anterior parietal peritoneum is irritated by a large or inflamed ulcer, local tenderness will result. It is rather to emphasize that tenderness can occur from stimulation of the ulcerated viscus itself.

The present experiments do not demonstrate in which part of the ulcerated stomach wall the pain sensitivity resides. They do show, however, that the pain sensitivity is within the wall of the viscus, and is not dependent on the involvement of the parietal peritoneum, the lesser omentum, or the retro-peritoneal tissues.

There is no need, therefore, to postulate a viscerosensory radiation to explain the epigastric tenderness in cases of peptic ulcer, but the presence of such a radiation is not disproved by the experiments. The viscerosensory radiation has for long been a theoretical conception, based largely on the inability to explain visceral tenderness in any other way, for the diseased viscus was believed to be insensitive to painful stimulation. Although the present results show that the ulcerated wall of stomach or duodenum is itself tender, it could be argued that in addition to the direct visceral tenderness there was also body wall tenderness, due to a viscerosensory radiation. The absence of hyperalgesia in the epigastrium does not support this view. Never-

theless, unless the patient is able to estimate whether the deep tenderness is diminished (or not) by abdominal wall anesthesia, there is no certain demonstration of the presence or absence of a viscerosensory radiation. Such measurement of the degree of pain introduces difficult subjective problems, and needs to be the subject of a separate investigation.

#### SUMMARY

- I. In patients with chronic peptic ulcer,
  - (i) the epigastric tenderness was abolished by splanchnic block,
  - (ii) the exposed ulcerated stomach or duodenum was sensitive to pressure, to pin prick, and to chemical stimulation. The non-ulcerated stomach wall was insensitive to these stimuli.
- II. It is concluded that the epigastric tenderness was not due to irritation of the anterior parietal peritoneum by the ulcer, but to pressure on the viscus itself. That is, the pain arose directly within the ulcerated viscus.
- III. There was no evidence of a viscerosensory radiation, but such a radiation is not disproved by these experiments.

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# HEMOPHILIA\*

PROBLEM OF SURGICAL INTERVENTION FOR ACCOMPANYING DISEASES  
REVIEW OF THE LITERATURE AND REPORT OF A CASE

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THE NUMBER OF CASES OF HEMOPHILIA who have undergone minor surgical procedures is very great and will not be a subject of review in this report. However, Birch<sup>1</sup> in a monograph on hemophilia in 1937 reported the following in regard to surgery in 113 cases of hemophilia studied. Analysis of the cause of death showed that the greatest number were due to hemorrhage following surgical procedures, all but one of which were operations of a minor nature. There can be no doubt that the great majority of hemophiliacs who undergo minor surgical procedures at the present time probably are brought through safely to recovery. Nevertheless, even the simplest operation still presents a serious problem calling for intensive treatment with prophylactic transfusions or injections of fresh plasma or Fraction I of Cohn before operation, with repeated use of these procedures postoperatively. In addition, local hemostatic measures should be used.

It is obvious that if minor surgical procedures are accompanied by such risk of fatal hemorrhage, major operations must be proportionately more hazardous. The site of trauma is probably the most important criterion of operability. If the operative site is exposed so that local hemostasis, pressure, and application of hemostatic substances can be employed, the chances of staunching the flow of blood are vastly increased. Thus Firor and Woodhall<sup>2</sup> successfully carried out the amputation of the thumb in a hemophiliac; Davidson and Levenson<sup>3</sup> have succeeded in skin grafting a hemophiliac with the help of thrombin; and Blalock<sup>4</sup> in 1932 amputated the arm of a proven hemophiliac. The occurrence of hemorrhage internally, either spontaneously or secondary to trauma, where local controlling measures cannot be continually applied presents a much more serious and difficult problem of management. A review of the literature in an attempt to collect opinions and results of major surgery in cases of hemophilia yields conflicting data. It is apparent that a wide discrepancy exists in the minds of the various authors as to the efficacy of surgery in acute emergencies, varying from almost complete lack of restraint

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in regard to operability to a feeling that no operation should be considered under any circumstances. Because of lack of unanimity of opinion as to the best course to follow in hemophiliacs who develop acute surgical conditions, a thorough search of the literature has been made with the hope that definite conclusions might be reached.

It is unfortunate that in many instances sufficient evidence is not presented by the particular author to allow an unequivocal diagnosis of hemophilia to be made. In view of the necessity of accurate diagnosis in attempting to formulate an opinion as to the advisability of surgery in hemophilia, we have eliminated from the analysis those reports in which there is any doubt of the specific nature of the hemorrhagic diathesis. The criteria established for the diagnosis of hemophilia are clear cut. These will be discussed further together with the reasons for exclusion of questionable cases. Those reports in which the diagnosis of hemophilia was unquestionable and those cases in which operative intervention for some associated disease was carried out will be reviewed in some detail.

In 1931 Emile-Weil<sup>5</sup> presented the results of surgical treatment of various disorders in an extensive article. The most outstanding case was one in which a gastro-enterostomy was performed because of a bleeding prepyloric ulcer. The operation was successful, hemorrhage being controlled by transfusions. In this case the coagulation time was two hours; clot retraction was good; bleeding time was three to seven minutes. Family history and past history were dubious. It seems probable that this was a case of true hemophilia. Another case reported by the same author involved the operative removal of a gangrenous appendix with recovery of the patient. This patient was five years of age; the family history, past history, and the sex of the patient are not given. The clotting time was 45 minutes; the bleeding time, nine minutes. Insufficient data are given to establish the diagnosis beyond doubt in this instance, although the prolonged coagulation time is highly suggestive.

The case of Blalock<sup>4</sup> reported in 1931, and already mentioned, was undoubtedly one of true hemophilia. However, here the application of local measures was possible; and although the procedure was major, it is not comparable to one accompanied by internal hemorrhage.

Cioran<sup>6</sup> in 1935 reported a case of acute appendicitis in a soldier shown to have hemophilia after operation. Bleeding of more than the usual amount was noted during operation, and later it was found that the coagulation time was four hours. Platelet counts were normal. It was determined that a maternal grandfather had a questionable hemorrhagic history and had died at an early age. The patient's past history revealed that he had had repeated nose bleeds and bruised easily during childhood. The patient was given two transfusions postoperatively without effect on the hemorrhage. However, intramuscular and intravenous injections of a substance called "Clauden" controlled the bleeding. This substance, "Clauden," was said by the author to be thrombokinase (thromboplastin) and was an aqueous extract of lung tissue. The patient gradually convalesced over a 35-day period. There is little doubt that this case was one of true hemophilia. It is rather startling

that hemorrhage should have been controlled by intravenous injections of thromboplastin, a procedure which has been shown in animals to be accompanied by intravascular thrombosis and death if given in large amounts.

Friedrich<sup>7</sup> in 1935 published an extensive article on the risk of operation in hemophilia. He cited several cases of his own and reviewed the literature, and arrived at some very definite conclusions. However, he made no attempt to present data supporting the diagnosis of hemophilia in these cases. He estimated the overall mortality of all major surgical procedures in hemophiliacs at 35 per cent. He felt operation in cases of appendicitis contraindicated except in the event of peritonitis, and cited two appendectomies which terminated fatally. He felt that the risk of hemorrhage following surgical intervention in appendicitis was greater than the risk of infection with conservative treatment (and this at a time before antibiotics and sulfonamides were available for clinical use.) He also found reports of six cases of retroperitoneal hematoma which were incorrectly diagnosed as acute abdominal emergencies, and were operated upon with uniformly fatal results. His opinion was that abdominal surgery should not be undertaken unless it was evident that death would ensue if surgical measures were not taken to alter the course. He pointed out that only in those cases where local measures could be applied was the prognosis favorable following surgery.

Mertz and Meiks<sup>8</sup> in 1938 reported a hemophiliac in whom nephrectomy was necessary because of a severe left hydronephrosis with infection. The diagnosis in this case was adequately established, and treatment was thorough and according to the accepted principles. This report will be quoted in some detail because of the striking similarity between the course of their patient and that of the case included in this paper. The patient was carefully studied and prepared preoperatively by means of sensitization to sheep serum and transfusion. The clotting time was brought down from 120 minutes to five and a half minutes prior to operation. Especial care was taken by the surgeons to obtain complete hemostasis, and no unusual bleeding was apparent at operation. Postoperatively, the patient's clotting time was six minutes and was kept down to low levels by repeated transfusions. There were no signs of bleeding for three days, and the patient appeared to be recovering. The drain which had been placed at operation was removed. However, the patient began to run a fever as high as 104.4°. On the fourth postoperative day, it was thought that free abdominal fluid had collected. The signs of this became more definite later; the intra-abdominal hemorrhage progressed in spite of repeated transfusions, and the patient died on the twelfth postoperative day due to hemorrhage and streptococcal septicemia. Autopsy showed a large hematoma at the site of the removed kidney with no evidence of bleeding from a major vessel but merely a slow ooze from the renal bed. The authors emphasized the fact that bleeding continued despite repeated transfusions and a clotting time at the lower limits of normal.

Vance<sup>9</sup> in 1939 reported four cases of surgical conditions in male patients with abnormal bleeding. One underwent a radical mastectomy because of carcinoma. He experienced some bleeding postoperatively which gradually

stopped without the necessity of transfusion. The clotting time in this patient was 16 minutes; family history and past history negative. The second patient had acute appendicitis. The clotting time in this case was only six minutes (method not given) and yet the diagnosis of hemophilia was made. Postoperatively the patient did well for five days but then bled continuously into the abdomen, in spite of blood transfusions, and died on the ninth postoperative day. The third case was one of acute appendicitis with a history very suggestive of hemophilia and a coagulation time of 18 minutes. Family history showed that a brother also had a hemorrhagic tendency. He was treated conservatively, with appendiceal rupture and subsequent localized peritonitis. The patient apparently bled considerably per rectum in spite of repeated transfusions and continued to do so for two weeks. Following this he rapidly improved. The fourth case was a brother of the above patient who also developed appendicitis. He was treated in the same manner as the previous case and died at the end of eight days. It is probable that these last two patients with appendicitis were true hemophiliacs. In respect to the first two patients, however, the diagnosis, if made on the basis of the data presented, is less certain.

Birch<sup>1</sup> in her monograph mentions one case of acute appendicitis in a true hemophiliac. Although the details of this case and the operation are not given, apparently the patient recovered from the operation but died one week later from postoperative pneumonia with hemorrhage from the lungs. It is doubtful that this case can be justly classified as an operative success.

A German military surgeon, Karitzky,<sup>10</sup> reported the treatment and course of a hemophiliac who had received severe combat wounds in October, 1939. There could be no doubt of the accuracy of the diagnosis in this case, the past history, family history and laboratory findings being classical of hemophilia. This marine had been injured by the explosion of a mine under his ship, steel splinters entering the left neck and hip regions. The steel fragment entering the hip region had penetrated, leaving a large wound of exit in the gluteal region near the anus. Hemorrhage was intense, and the patient lapsed into shock. Débridement was carried out, the fragment removed from the neck with closure; and the gluteal wound was packed with iodoform gauze. The cervical wound healed normally. On the fifth day after injury, the patient began to lose large amounts of blood from the gluteal wound. He continued to bleed for 24 days and became dangerously anemic in spite of repeated transfusions and injections intramuscularly of substances such as Redoxon, Koagulen, Gelatine, Clauden, etc. A putrid wound infection developed. Massive transfusions and pressure dressings finally controlled the bleeding to a large degree, but oozing from stitch wounds and needle punctures continued for some time. The patient finally recovered. This example of protracted uncontrollable hemorrhage from a wound which was amenable to local measures in a hemophiliac treated intensively with blood transfusions again demonstrates the serious difficulties which may be encountered in bringing about hemostasis. However, the fact that no internal operative procedures were performed in this case removes it from that type of operative intervention with which we are concerned.

In addition to those reports reviewed, there have been numerous others of major surgery performed in patients suffering from some hemorrhagic diathesis. The nature of the surgical condition, the results of surgery, and the data upon which the diagnosis of hemophilia was made are presented in Tables 2 and 3. It was our opinion that insufficient information was presented by the authors for the diagnosis of true hemophilia in these instances. The criteria necessary for the diagnosis of this particular hemorrhagic diathesis and the reasons for excluding these cases will be discussed in more detail later.

#### PRESENTATION OF A CASE

E W, a 27-year-old single white male, was admitted to Strong Memorial Hospital October 4, 1947. He had been awakened the previous morning by a crampy epigastric pain which was followed by nausea and vomiting. The pain persisted after he had vomited, was generalized throughout the abdomen but was slightly more pronounced in the right lower quadrant. He had taken a dose of cascara which he had promptly vomited. In spite of a small but normal bowel movement that day, his pain became steadily worse. On the morning of admission the pain was localized in the right lower quadrant, was constant and rather dull and aching in character. He had felt feverish but had no other complaints.

*Past History.* The patient had been seen in this hospital in 1927 at the age of seven with a history of having bled profusely and bruised easily since early childhood. The coagulation time of whole blood was found to be 4 hours, and a diagnosis of hemophilia was made at that time. He had had numerous hospital admissions and clinic visits from that time forth because of hemoarthrosis, hematuria, and hemorrhage from the gums. He was intensively studied in 1940 and again in 1945, and had received extensive orthopedic care. As a result of the use of fresh plasma and whole blood and of careful orthopedic management, he had been able to work fairly regularly and to walk during much of this time. He had been free of bleeding during these periods of therapy for as long as one year. Fresh whole blood or plasma always lowered the coagulation time. In spite of 6 whole blood transfusions and 100 plasma transfusions from 1927 to the present time, no refractory state ever developed. A detailed summary of the laboratory findings is found in Table I.

TABLE I

	1927	1939	1940	1941	1945
Coagulation time	40'	30'	70'	85'	36'-72'
Clot retraction	good	good	good	good	good
Bleeding time	3 25'	1 5'			
Prothrombin concentration (% normal)					
Calcium		normal 10 mg per cent			80 per cent 10 4 mg per cent 0 2 Gm. per cent 76 mg per cent
Fibrinogen.	.				
Vitamin C.		..			
Platelets	250,000	normal no	normal no	normal no	normal no

*Family History* revealed that a maternal great-uncle had "bled to death," but no other important family history could be obtained. This is shown in Figure I.

*Physical Examination:* revealed a moderately well developed, somewhat dehydrated 27-year-old white male in moderate distress. There was a fine macular rash over the anterior chest, and there were ecchymotic areas over the left hand. His temperature was 101.3° F. The blood pressure and pulse were normal. The pertinent physical findings were limited to the abdomen and the extremities.

The abdomen was slightly distended, tender in the epigastrium and more so in the right lower quadrant where there was also spasm and rebound tenderness. There was bilateral rectal tenderness, more marked on the right. Both ankles and both knees showed old joint deformities.

The white blood count was 14,200 per mm.<sup>3</sup> at the time of admission. The urine was negative except for a strong acetone reaction. In view of this patient's known hemophilia, it was decided to employ conservative measures even though it was felt that he had acute appendicitis. Accordingly he was given penicillin 100,000 units intramuscularly every three hours, was hydrated, and given 5 grams of sodium sulfadiazine in 1000 cc. of saline intravenously. It was decided to reduce the coagulation time, which was found to be 60 minutes. Four-tenths Gm. of Fraction I of Cohn ("Antihemophilic globulin") and 100 cc. of freshly prepared plasma were administered intravenously. The coagulation time was 11 minutes when observed 20 minutes after this treatment and was 15 minutes 4 hours later.

After a period of observation of 10 hours, during which the leukocytosis, the fever and the symptoms increased, it was decided to operate. This decision was reached after much deliberation and in view of the normal coagulation time, although it was felt that there was considerable risk involved in the procedure.

*Operative Note.* Under ether anesthesia, the abdomen was opened through a small McBurney incision. No unusual bleeding was encountered. The peritoneal cavity contained a small quantity of cloudy fluid which on culture was found to contain *E. Coli*. The cecum was delivered into the wound without difficulty. The appendix lay in a retrocecal position with its tip beneath the ileocecal valve and surrounded by fairly dense adhesions. These adhesions were broken up by blunt dissection, but the tip of the appendix could not be mobilized. A small Weir extension was made for better exposure, in spite of which the appendix could not be delivered. It was thought unwise to mobilize the cecum by incising its lateral attachments because of the danger of hemorrhage. For this reason the appendix was removed in a retrograde fashion partly by blunt dissection. Its wall was necrotic at the site of two fecoliths near its mid-portion. The stump was ligated with a surgeon's knot of 000 silk and inverted beneath two purse string sutures. There was a moderate ooze from the appendiceal bed which could not be visualized. It did not appear to be dangerous in quantity and was not felt to be arising from any sizable vessel. It was satisfactorily controlled with a pack of gelfoam. Drainage was discussed but not carried out. The abdominal wall was closed in layers with silk, taking great pains to ligate or cauterize the smallest bleeding points. In spite of this care, there was minimal ooze from the subcutaneous tissue.

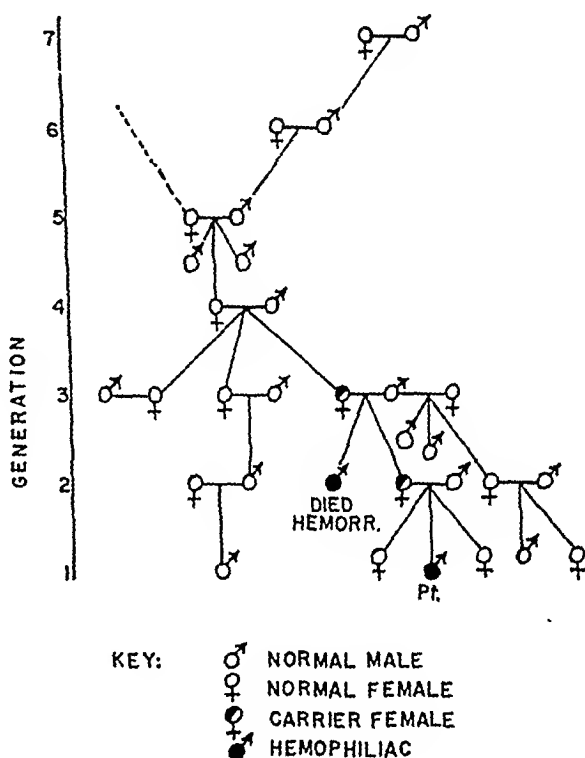


FIG. 1.—Graphic representation of patient's family history.

The patient's condition was good at the close of the procedure. Pathologic examination of the specimen confirmed the clinical diagnosis of acute appendicitis.

During the operation the patient received 500 cc. of fresh compatible whole blood, and one hour later he was given 0.2 Gm. of Cohn Fraction I and another 500 cc. of fresh compatible whole blood. He was placed on Wangenstein suction. Careful check was kept of the coagulation time (the Lee-White method, performed at 37.5° C, and by the same person as often as possible) and the plasma and whole blood specific gravity. These, in addition to the antihemophilic therapy, are summarized in Figure 2. At no time could a circulating anticoagulant be demonstrated similar to that described by Craddock and Lawrence.<sup>10</sup>

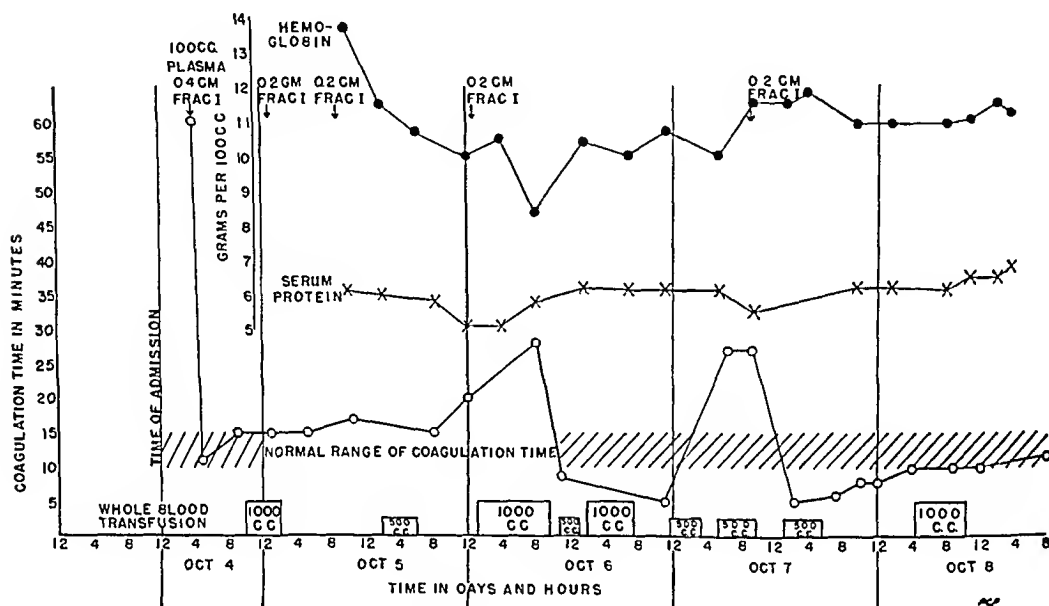


FIG. 2.—Course of patient in hospital showing amounts of antihemorrhagic treatment, response of coagulation time, and degree of serum protein, and hemoglobin deficiency.

Penicillin was continued, but because of the presence of albuminuria and microscopic hematuria, sulfadiazine was discontinued. A conscientious attempt was made to maintain a normal fluid and electrolyte balance.

In spite of the fact that the coagulation time was kept almost entirely within normal limits, the patient continued to lose blood into his peritoneal cavity and into his abdominal incision. His abdomen became distended to the point where he had severe respiratory embarrassment, and on the fourth postoperative day it became necessary to perform an abdominal paracentesis, 600 cc. of bloody, incoagulable fluid being removed. The patient experienced some relief, but later in the day he was again severely dyspneic; and there were signs of atelectasis. The abdominal wound was partially opened under sterile precautions and 600 cc. of fluid, defibrinated blood removed, this later proving to have been extraperitoneal.

On the evening of the fourth postoperative day, the patient's respiratory embarrassment became extreme; there were signs of bilateral pleural effusion, and thoracentesis was performed. After 150 cc. of bloody fluid had been withdrawn, the patient's respirations ceased. Artificial respiration and intravenous coramine were of no avail, and the patient expired.

*Post mortem Examination:* revealed pulmonary edema, bilateral hemothorax, a large blood clot in the appendiceal bed extending along the right peritoneal gutter from the pelvis to the liver. There was no evidence that the bleeding had come from any large bleeding point. There was also a tremendous hematoma at the site of the abdominal wound, not communicating with the peritoneal cavity.

### DISCUSSION

In reviewing the literature on this subject, we have attempted to analyze critically each report in order to determine which cases represented operation in true hemophilia. The criteria selected by us for the establishment of the diagnosis of hemophilia in the individual cases reviewed are the following (see Table II.) (1) Laboratory findings showing definite prolongation of the clotting time as the only abnormal test of those routinely performed pertaining to the hemostatic mechanism. (2) Positive family history (although occurrence of sporadic spontaneous cases is occasionally found.) (3) A past history typical of that exhibited by the majority of hemophiliacs. (4) Occurrence in a male. These criteria are taken because the majority of the reports do not include detailed clinical and laboratory data in regard to the question of hemophilia. Attempt has been made to weigh the facts given in each instance and determine whether or not they permit the diagnosis of hemophilia.

It is recognized that there is great variation in the technic and results obtained in tests performed in regard to the clotting mechanism. Nevertheless, the one laboratory abnormality necessary for the diagnosis of hemophilia (in the untreated case) is a prolonged clotting time of the blood. In most instances the technic used for this test was not stated, but unless a definite prolongation over the stated limits considered normal by the author is recorded, the laboratory data cannot be regarded as diagnostic unless accompanied by other tests supporting the contention. In true hemophilia all the other tests routinely performed pertaining to coagulation time are normal (*i.e.*, prothrombin time, bleeding time, tourniquet test, platelet count, and clot retraction, and determinations of calcium and fibrinogen concentrations.)

In those cases reported, if the laboratory data are of questionable significance, the other criteria are studied. If there is a definite positive family history, that is, reliable evidence of hemorrhagic disease in male members of previous generations on the maternal side, then this is considered to support the diagnosis of hemophilia in the face of positive or suggestive laboratory data. Here again in many reports, the family history was either not mentioned or else was not elucidated in questionable instances. It is recognized that sporadic cases occur in whom no family history is detectable no matter how far back it is investigated. For this reason a negative family history does not exclude the diagnosis, but a positive one is good supportive evidence. In regard to the criterion of past history in the particular cases reviewed, it is felt that most hemophiliacs present stories of previous hemorrhagic phenomena which are fairly typical of the disease. Such occurrences in the past history as repeated hemarthrosis, subcutaneous bleeding after slight trauma, spontaneous bleeding per rectum or hematuria without the



presence of pathologic lesions, and prolonged bleeding from minor cuts are usually cited by the hemophiliac. The absence of such a past history by no means excludes the diagnosis, but its presence lends support in questionable cases. However, such symptoms can occur in other hemorrhagic diseases, and for this reason a positive past history alone cannot be used as the sole criterion for the diagnosis. The sex of the patient was not given in all reports. As far as is known at present, hemophilia occurs only in males. This has not always been accepted as true in the past. Therefore, in the older reports unless the sex is definitely stated or inferred, doubt is cast on the validity of the diagnosis of hemophilia.

#### ANALYSIS OF REPORTED CASES OF MAJOR SURGERY IN HEMOPHILIA

As shown in Table II extensive surgical procedures have been successful in areas where local measures could be applied to control blood loss. However, in regard to abdominal surgery, the chances for a satisfactory outcome are much less. If one accepts all cases reported as being true hemophiliacs, it would appear that the risks of major operation are not more extreme than would be indicated in the past.

Thus, of 15 major operations performed in areas of the anatomy where the application of pressure and local hemostatic agents was not possible, there were 11 recoveries and four deaths, or a mortality of 26.7 per cent. This mortality is close to that estimated by Friedrich for operations of this type in hemophilia. The percentage of recoveries is higher than might be anticipated. Indeed, from analysis of the cases, excluding those not proven to be true hemophilia, it is evident that the percentage is less optimistic. Of the 15 cases reported, there are only four which, on the basis of the facts presented, fulfill the criteria needed for the unequivocal diagnosis of hemophilia. Of these four, there were two fatalities which gives a mortality of 50 per cent. If our case is included, the mortality is raised to 60 per cent. All of these fatal cases received adequate treatment with transfusions. It would seem, therefore, that major surgery in cases of hemophilia of the type where local hemostatic measures cannot be utilized is accompanied by an expected mortality rate which is much greater than that which is usually indicated by the literature on this subject.

In regard to treatment of acute appendicitis *per se* in cases of hemophilia, the literature reviewed by us discloses 11 reports. Eight of these were operated upon and three treated conservatively. Of the eight receiving operative treatment, there were six recoveries and two deaths, or a mortality of 15 per cent. However, among the eight undergoing appendectomy, there were only two who fulfilled the criteria needed for the unequivocal diagnosis of hemophilia. Of these two, one died, and one recovered, thus giving a mortality of 50 per cent following operation. Our case would raise the mortality to 66.6 per cent.

On the other hand, there were three cases of true hemophilia with appendicitis treated conservatively. Two of these were definite instances of acute

TABLE II.—*Reported Cases of Major Surgery in Hemophilia.*

Associated Disease	Authors	Operation	Outcome	Criteria of Diagnosis of Hemophilia			Positive Diagnosis Hemophilia
				Laboratory Data	Family History	Past History	
Gangrene, arm	Blalock <sup>4</sup>	Amputation	Recovery	+	+	+	Yes
Trochanteric hematoma	Emile-Weil, <sup>11</sup> Scemama	Incision and drainage	Recovery	+	+	+	Yes
Carcinoma of breast	Vance <sup>9</sup>	Radical resection	Recovery	±	O	±	Yes
War wounds	Karitzky <sup>10</sup>	Debridement	Recovery	+	+	+	Yes
		Removal of foreign body					
Tuberculous knee	Friedrich <sup>7</sup>	Exploration of knee	Recovery	O	+	O	Yes
Bladder polypi,	Mathe and Mitchell <sup>12</sup>	Polypectomy	Recovery	—	—	±	Yes
prostatic median bar		Fulguration of median bar					
Prostatic hypertrophy	Hinnman <sup>13</sup>	Perineal prostatectomy	Recovery	—	±	+	Yes
Hydronephrosis with infection	Mertz, Melks <sup>3</sup>	Nephrectomy	Death	+	+	+	Yes
Peptic ulcer with hemorrhage	Emile-Weil <sup>13</sup>	Gastro-enterostomy	Recovery	+	±	+	Yes
Pre-pyloric ulcer with hemorrhage	Wosnesensky <sup>14</sup>	Gastric resection	Death	O	O	O	Yes
Appendicitis	Emile-Weil <sup>13</sup>	Appendectomy	Recovery	+	O	O	Yes
Tonsillitis and appendicitis	Hays <sup>15</sup>	Tonsillectomy	Recovery	—	O	O	Yes
		Adenoidectomy					
Appendicitis	Vance <sup>9</sup>	Appendectomy	Death	±	O	O	Yes
Appendicitis	Birch <sup>1</sup>	Appendectomy	Death*	+	+	+	Yes
Appendicitis	Prima <sup>16</sup>	Appendectomy	Recovery	O	O	O	Yes
Appendicitis	Cioran <sup>6</sup>	Appendectomy	Recovery	+	+	—	Yes
Appendicitis	Hipsley <sup>17</sup>	Appendectomy	Recovery	O	±	+	Yes
Appendicitis	Paz <sup>18</sup>	Appendectomy	Recovery	O	—	+	Yes
Ruptured spleen	Friedrich <sup>7</sup>	Splenectomy	Recovery	O	+	O	Yes
Gastro-intestinal bleeding	Friedrich <sup>7</sup>	Gastric resection	Recovery	O	+	+	Yes
Appendicitis	This report	Appendectomy	Death	+	+	+	Yes

\* Patient survived operation one week, but died with postoperative hemorrhagic pneumonia.  
Symbols: + = Positive findings. — = Negative Findings. ± = Questionable or inadequate findings. O = Data not given.

appendicitis. The other patient, that of Platou<sup>20</sup> was felt at first to have appendicitis with intestinal obstruction. The latter disappeared after Wangenstein suction was instituted, and the patient recovered. The authors later felt that this patient probably did not have acute appendicitis but rather a hemorrhage into the submucosal area of the small intestine. Therefore, the total number of cases of appendicitis in hemophiliacs reviewed by us who received nonoperative treatment is two, with one death.

TABLE III.—*Results of Treatment of Appendicitis in Hemophilia.*

Author	Type of Treatment	Outcome	Criteria of Diagnosis of Hemophilia			Sex	Positive Diagnosis Hemophilia
			Laboratory Data	Family History	Past History		
Hipsley <sup>17</sup>	Appendectomy	Recovery	O	±	+	♂	
Emile-Weil <sup>18</sup>	Appendectomy	Recovery	+	O	O	O	
Hays <sup>18</sup>	Appendectomy	Recovery	—	O	O	♂	
Vance <sup>9</sup>	Appendectomy	Death	±	O	O	♂	
Cioran <sup>6</sup>	Appendectomy	Recovery	+	+	—	♂	Yes
Birch <sup>1</sup>	Appendectomy	Death*	+	+	+	♂	Yes
Prima <sup>16</sup>	Appendectomy	Recovery	O	O	O	♂	
Faz <sup>18</sup>	Appendectomy	Recovery	O	—	+	♂	
This report	Appendectomy	Death	+	+	+	♂	Yes
Vance <sup>9</sup>	Non-operative	Recovery	±	+	+	♂	Yes
Vance <sup>9</sup>	Non-operative	Death	±	+	O	♂	Yes
Platou <sup>20</sup>	Non-operative	Recovery**	+	+	+	♂	Yes

\* Patient survived operation one week but died with postoperative hemorrhagic pneumonia.

\*\* The diagnosis of appendicitis was not felt to be definitely established by the author.

Symbols: + = Positive findings.

— = Negative findings.

± = Questionable or inadequate findings.

O = Data not given.

The small number of reported cases of acute appendicitis in hemophiliacs treated by either operative or nonoperative means does not allow any valid comparison of expected results. Nevertheless, it is obvious that the dangers of uncontrollable fatal hemorrhage following internal operative intervention multiply many times the operative risk. Most statistics on the subject place the present mortality rate following acute appendicitis with rupture and peritonitis at 10–15 per cent in otherwise normal individuals.<sup>21-24</sup> It is not known how much the presence of hemophilia would increase the dangers of peritonitis of appendiceal origin. Certainly there is no good evidence to suggest that hemophiliacs cannot handle infectious processes as well as normal individuals. From our review of the literature, we believe the mortality rate following appendectomy in hemophiliacs is around 50 to 60 per cent. It is probable that the chances of death due to postoperative hemorrhage outweigh the expected mortality associated with the nonoperative treatment of appendiceal rupture and peritonitis.

The hemophiliac presented by us had been followed in this hospital since the onset of his hemorrhagic difficulties and had been the subject of extensive investigative and therapeutic procedures. It was well known that he obtained marked benefit from plasma injections, and he had been kept entirely free of

hemorrhagic phenomena for long periods of time without ever showing evidence of becoming refractory. As shown in the case report, when he was given blood, his clotting time fell rapidly to normal. He was of the optimal age group for surgery and possessed the physical stamina to withstand such a procedure. It was our hope that if operation were necessary, the coagulation mechanism could be augmented by transfusion or injections of fresh plasma or Fraction I of Cohn to such an extent that severe hemorrhage could be controlled.

The persistence of hemorrhage in this patient in spite of a normal coagulation time demands further comment and brings to mind several considerations in regard to the present concept of the fundamental defect in hemophilia. It is the belief of many investigators in this field at the present time that the underlying abnormality in hemophilic blood is a deficiency or lack of a plasma factor necessary for coagulation to take place in the normal span of time. This factor has been shown, by numerous workers,<sup>25-27</sup> to be present in normal blood but deficient in hemophilic blood. Howell<sup>27</sup> worked extensively with this factor which he called "plasma thromboplastin." Quick<sup>28</sup> feels, as did Howell, that this factor represents an inactive form of thromboplastin which is normally present in the blood and is activated by an enzyme released from platelets when coagulation begins. The factor has more recently become available in purer form and in greater amounts through the fractionation of plasma by Cohn and co-workers at Harvard. The active principle is contained in greatest concentration in Fraction I and Fraction III, subfraction 2 of Cohn's classification. It has been termed "antihemophilic globulin" by Lewis, Tagnon, *et al.*<sup>29</sup> and has been investigated extensively by these and other workers.

There is no question that "antihemophilic globulin" in very small amounts has a beneficial effect on the clotting mechanism of hemophiliacs. This effect is demonstrated by the sharp fall in coagulation time to normal values within a very short time after it has been injected intravenously. However, its effect is no greater and of no more permanency than the beneficial response elicited by whole blood or plasma. This is as might be anticipated since each type of treatment merely supplies a factor which is deficient in hemophilic blood. This factor, necessary for coagulation to occur in the normal span of time, is apparently used up over a period of 12 to 48 hours, so that at the end of this time, the deficiency again exists; and the coagulation time again becomes prolonged.

The fact that the deficiency of "antihemophilic globulin" was erased by the concerted treatment given this patient is borne out by the shortening of the coagulation times to normal levels. The continuation of hemorrhage, even in the face of the normal coagulation time of the blood, forces one to the conclusion that the mere deficiency of the substance "antihemophilic globulin" cannot be the sole abnormality of coagulation in hemophilia. There are other, perhaps more subtle changes from normal in the coagulation mechanism which cannot be measured by the tests of blood coagulability routinely used. It is well to remember, therefore, that the actual time consumed by clot formation in the test tube is by no means an accurate measure of the ability of the hemostatic mechanisms to control blood loss.

Other recent investigations into the clotting mechanism have made it highly suggestive that the present concept is incomplete. Attempt will not be made to review these advances, but it is becoming apparent that there are factors concerned in the first stage of clotting that heretofore have not been appreciated. Thus Ware *et al.*<sup>30</sup> believe an activator globulin (AC globulin) is necessary for prothrombin activation; Milstone<sup>31</sup> postulates a prothrombokinase which is activated in the presence of calcium ions to thrombokinase (thromboplastin) and which in turn activates prothrombin; Owren<sup>32</sup> reports a principle designated as Factor V which is essential for rapid prothrombin conversion to thrombin, and Quick<sup>33</sup> has designated two components of prothrombin (A and B) as well as a "labile factor" which is also necessary for coagulation to occur in the normal time. It is probable that these various factors are closely related, if not the same. It is not known where these factors fit into the present formula of clotting; there is little doubt that the speed of prothrombin conversion and hence the speed of clotting is greatly influenced by their presence. These investigations as well as others such as those of Ferguson<sup>34</sup> indicate the existing confusion and inadequacy of knowledge concerning blood coagulation. The importance of these advances in regard to the treatment of hemophilia are unknown at present. Certainly this case would indicate that a mere deficiency of "antihemophilic globulin" does not explain the blood loss in all cases. It is likely that the normal fresh blood given to this patient in large quantities contained an adequate amount of all the factors described by various authors as necessary for coagulation. It is evident that whatever the defect may be which causes hemorrhage in hemophilia, it cannot always be corrected, even temporarily, by supplying the patient with those factors concerned with clotting as they exist in normal blood.

The main points to be emphasized with regard to this case are the following: First, and most important, the coagulation time of the blood cannot be taken as a measure of the adequacy of the hemostatic mechanism in the hemophilic patient. Howell<sup>27</sup> has stated, "at present the one pathologic condition in hemophilia that is definitely established and that is directly connected with the hemorrhage is the prolonged clotting time of blood. Those who have had the widest experience with hemophilic patients believe the severity of the disease is in general proportional to the delay in coagulation." This feeling has been almost generally accepted in regard to the disease. The main object of all therapy up to the present time has been to lower the coagulation time of the blood. This patient demonstrates clearly that coagulation time alone can be used neither as the sole measure of the severity of the hemorrhagic tendency nor as a test of the response of the hemophiliac to treatment. There can be no doubt that the coagulation time of this patient's blood was usually maintained within limits which are considered normal, and yet hemorrhage continued with loss of the blood as rapidly as it was replaced.

The second point to be emphasized is the difficulty in choosing a case for operation. By all the accepted standards this hemophiliac met most of the requirements for operability, as well as any patient suffering from this disease

could meet them. And yet death resulted in spite of most intensive anti-hemorrhagic treatment.

The third point to be stressed is the infinite difference between controlling postoperative hemorrhage from areas that are exposed and amenable to local measures and controlling hemorrhage from internal areas. It is our feeling that if the site of bleeding cannot be treated with pressure, application of hemostatic substances, and other local measures, then the chances of recovery from surgery are poor.

In view of the unfortunate results of surgery in this case and the unconvincing reports of the efficacy of major surgery in hemophiliacs as gathered from the literature, it is our belief that conservative medical treatment is the course of choice in these cases unless it becomes clearly evident that death will ensue if surgery is not undertaken. The dangers of uncontrollable hemorrhage following surgery outweigh the dangers of generalized peritonitis and subsequent fatal infection, especially with the modes of controlling infection now at hand. The only existing well established means of combating hemorrhage in these cases is to give the patient fresh whole blood transfusions, injections of fresh or lyophile plasma, or the substance known as "antihemophilic globulin" as contained in Fraction I of Cohn. Each of these three forms of therapy accomplishes the same end. Each supplies the hemophiliac with a deficient substance necessary for coagulation to take place in the normal span of time. When the hemophiliac is given this substance by any of the means described, the coagulation time of the blood is reduced to normal. And yet, as demonstrated by this case, correction of this deficiency with a concomitant reduction in the clotting time to normal does not always promote hemostasis. This lack of response on the part of the hemophiliac's clotting mechanism to present modes of therapy in all instances further increases the dangers associated with any type of major surgical procedure undertaken in patients with this disease.

#### SUMMARY AND CONCLUSIONS

1. A review of the available medical literature reveals that the reported instances of internal operative procedures in patients with hemophilia require careful analysis. Many of the cases are accompanied by data that are inadequate for the diagnosis of this hemorrhagic diathesis.

2. The mortality following internal surgery in established cases of hemophilia is relatively high. Of four previously reported cases in whom the diagnosis of hemophilia was unequivocal, two died from hemorrhage following operation while two recovered. The other eleven reports of internal surgical procedures in patients with bleeding tendencies were excluded from this analysis because of inadequate basis for the diagnosis of hemophilia. If these were included, the total number of recoveries following operation would be eleven with only four deaths, or a mortality rate of 26.7 per cent, a figure we believe to be erroneously low.

3. A case of unequivocal hemophilia is presented with the complication of acute appendicitis. The patient received intensive antihemorrhagic therapy,

but despite a normal clotting time he continued to bleed profusely and expired four days postoperatively.

4. A discussion of the significance of continued hemorrhage in the presence of a normal *in vitro* clotting time and of its relation to the fundamental defect in hemophilia is presented. Emphasis is placed on the failure of the coagulation time to indicate the severity of the hemorrhagic tendency or the degree of response to treatment, the difficulty in choosing a suitable case for operation, and the great difference in controlling internal hemorrhage as opposed to bleeding from an external site.

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# REDUCTION OF INTUSSUSCEPTION BY BARIUM ENEMA\*

## A CLINICAL AND EXPERIMENTAL STUDY

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IN 1836 THERE APPEARED in the American Journal of the Medical Sciences an account<sup>1</sup> of "A Case of Introsusception in Which an Operation Was Successfully Resorted to by John R. W. Wilson, M.D., of Rutherford County, Tennessee in December, 1831." The author concluded, "His recovery was rapid and entire. . . . The success of this case in which the operation was so long deferred, and at last performed under such unfavorable circumstances, warrants the propriety of resorting to it in the disease, and proves that relief may occasionally be afforded by this means when all others have failed."

Seventy-five years later, in 1906, operation was still so uncertain and dangerous that Harvey Cushing, as a house officer, wrote a note in the history of a child with intussusception, stating that operation was postponed with the hope that sphacelation might take place and the sphacelus be passed entire per rectum. As far back as 1784 Nuck<sup>2</sup> had diagnosed intussusception in a man of 50 years who was successfully operated upon by an unnamed surgeon. In 1825 Fuchsius<sup>3</sup> operated successfully for intussusception in a man of 68. Wilson's is the third successful instance in the literature and the first in this country. A few other operative cases, all fatal, had been reported by 1871 when Jonathan Hutchinson<sup>4</sup> performed the first successful operation for intussusception in a child, a baby of two years. Until this time the disease had been treated either expectantly, waiting for gangrene or sphacelation of the intussusception, or by rectal instillations. With this background Hirschsprung<sup>5</sup> of Copenhagen in 1876 reported his experiences with the treatment of intussusception by hydrostatic pressure. This method is older than any operative one. Hippocrates advised forced injection of water or air into the intestines in all forms of ileus, and several authors in the early nineteenth century advised and used clysters successfully. Others used bellows, or connected hydrogen sulfide generators with the rectum, or inserted effervescent powders. Still others passed long bougies to perform a direct reduction, or stimulated the intussusceptum with electricity, or tried to shrink it with cold water or hypertonic saline solution. By 1905<sup>6</sup> Hirschsprung was able to report on 107 personal cases of intussusception. His results were so superior to those previously reported that his contemporaries doubted his conclusions. He was forced, in self-defense, to publish a table listing each of his 107 cases. He presented a 35 per cent mortality in a disease which up to that time was fatal in almost 90 per cent of the cases. In 84 patients treated by Hirschsprung with

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enema alone, the mortality was 23 per cent. These figures compare favorably with those from the Johns Hopkins Hospital in the period from 1929 to 1938, more than 25 years after Hirschsprung.

Our interest in intussusception was aroused in 1933 by the paper of Dr. E. H. Miller<sup>7</sup> of Chicago who described his own poor results (45 per cent mortality in 20 cases) and referred to the remarkable results of Hipsley in Australia with reduction of intussusception by hydrostatic pressure. The method of reduction by hydrostatic pressure was systematized by the Danish school, Hirschsprung<sup>5</sup> and his successors, Kock and Oerum,<sup>8</sup> and Monrad.<sup>9</sup> All of these also practiced, to varying degrees, manual disinvagination of the intussusception through the intact abdominal wall. In 1913 the first report of intussusception diagnosed by roentgenography was made by Lehmann.<sup>10</sup> In 1927 Pallin and Olsson<sup>11</sup> in Sweden, Retan<sup>12</sup> in the United States, and Pouliquier<sup>13</sup> in France all reported reductions by barium enema under fluoroscopic control. The Australians continue to use simple saline enemas, but the use of the barium enema has gained great popularity in Scandinavia and South America. In this country, in England, and in Germany the use of hydrostatic pressure has never been accepted. It is a remarkable fact that surgeons, reporting in 1930 and 1940 a 20 and 30 per cent mortality for the treatment of intussusception, scorn the non-operative methods which had a lower mortality in 1890 and 1900 and which, in 1926, gave a mortality of as low as 5 per cent in 100 consecutive cases treated by Hipsley.<sup>14</sup> Hipsley, be it noted, took up the use of hydrostatic pressure to improve his mortality of 8 per cent with operative treatment. One of Hipsley's papers, published in 1935,<sup>15</sup> is of particular interest and should satisfy those who maintain with Ladd<sup>16</sup> that the situation is different in Australia because there an entire generation of medical men has been intensely interested in intussusception through the work and teaching of Sir Charles Clubbe.<sup>17</sup> Hipsley reported on this occasion 486 cases of intussusception treated by 10 surgeons with a mortality of 11 per cent. Three of the 10 surgeons always attempted a preliminary reduction by saline enema and had a mortality of 9.8 per cent. The other seven surgeons operated on all patients without injection and had a 14 per cent mortality. This is a significant difference in a large series of patients treated in the same period of time at the same hospital.

Table I tabulates the mortality from 10 American and British clinics, with figures running from 60 per cent to 8.3 per cent. The lower figures are all in recent years, but mortalities of 40 and 50 per cent are common 20 and 30 years after Hirschsprung's day. Table II, by contrast, shows the mortality in those clinics using hydrostatic pressure. There is a striking difference, the range being much lower with mortalities years ago of 5 per cent, 7 per cent, and 9 per cent. Most of the fatal cases were also operated upon; accordingly, it is to be expected that with modern operative and supportive methods even lower mortalities can be expected. It must also be remembered that mortality rates alone do not tell the story. The morbidity is many times higher in the operative cases—wound infections, distention, fever, postoperative intestinal obstructions (sometimes several bouts in the same child over a period of years).

The hospital stay of the operative patient is much longer. The average hospital stay in our 27 patients treated primarily by enema was 9.2 days, as opposed to an average hospital stay of 32.4 days for 16 others treated during the same period primarily by operation.

TABLE I. *Mortality from intussusception treated primarily by operation. Note the relatively high mortality rates compared with those in Table II.*

Author	Primary Method	Period	Number of Cases	Per Cent Mortality	Source
Kahle	Operation	1904-1938	150	52	New Orleans
		1928-1938	59	30.5	(Charity)
Perrin & Lindsay	Operation	1903-1920	400	34.8	London
		1915-1920	113	22.0	(London Hospital)
Close	Operation	1904-1927	363	31	London
Ladd & Gross	Operation	1908-1939	484	?	(Guy's Hospital)
		1908-1912	?	59	Boston
		1928-1932	?	14	(Children's Hospital)
		1939	12	0	
Peterson & Carter	Operation	1908-1932	64	30	New York
		1922-1932	21	10	
Wakeley & Atkinson	Operation	1920-1929	121	10	London
					(King's College)
Gordon	Operation	1917-1938	44	23	New Haven (Yale)
Miller	Operation	1934	20	45	Chicago
Gibbs	Operation	1927-1942	91	30	Cincinnati General
		1937-1942	36	8.3	
Mayo & Woodruff	Operation	1941	55	23.6	Mayo Clinic

TABLE II.—*Mortality from intussusception treated primarily by hydrostatic pressure. Note the low mortality rates and the early dates at which these were achieved.*

Author	Primary Method	Period	Number of Cases	Per Cent Mortality	Source
Hirschsprung	Saline enema	1871-1905	100	35	Copenhagen
	Manual disinvagination				
Clubbe	Enema or operation	1901-1926	834	14.5	Australia
Hipsley	Saline enema	1926	100	5	Australia (Sydney)
Hipsley	Saline enema	1921-1934	171	9.8	
	Operation	1921-1934	315	14	Australia (Sydney)
Sjöström	Barium enema	1927-1934	38	16	Sweden (Lund)
Hellmer	Barium enema	1933-1942	110	7.3	Sweden (Lund)
Nyborg	Barium enema	1930-1941	108	7	Sweden (Lund)
	Barium enema	1935-1941	84	5	

Table III records the mortality from intussusception at the Johns Hopkins Hospital since its opening. From 1893 to 1928, long after Hirschsprung's death and after Clubbe's report from Australia of 834 cases seen over 25 years with a mortality of 14.5 per cent, a line of surgeons at the Johns Hopkins Hospital, including Halsted, Cushing, Follis, Heuer and others, had a mortality of 44 per cent. The next group of surgeons in the period 1929 to 1938 lost 14 out of 44 patients, a mortality of 32 per cent, and the last group, 1939 to 1947, lost 5 out of 48, a mortality of 10.4 per cent. Of these 48 patients, however, 27 were treated primarily by enema with no deaths, and 21 primarily by operation with five deaths or a 24 per cent mortality. It is only fair to note that

# INTUSSUSCEPTION BY BARIUM ENEMA

there has been some selection of cases in these two groups. Beginning in 1939 the senior author has administered a barium enema to every patient with intussusception whom he has seen. However, some residents chose to do primary operations on the patients they judged to be the sickest, whereas others operated on all patients with intussusception.

The barium technic is as follows: As soon as the presumptive diagnosis of intussusception is made, the child is taken to the fluoroscopic room. At the same time, if it is at night, the operating room is alerted. In the fluoroscopic room, without anesthesia, an unlubricated Foley bag catheter is inserted in the rectum. The bag is distended with 20 to 40 cc. of air according to the size of the patient, and barium is permitted to run in from a height of three feet. (Fig. 1.) It is important not to lubricate the catheter as it will then be more easily retained. In addition, it is essential for an assistant to squeeze the buttocks together throughout the procedure. The barium usually runs rapidly

TABLE III.

## THE JOHNS HOPKINS HOSPITAL

### MORTALITY FROM INTUSSUSCEPTION

1893 - 1928

24/54 PATIENTS DIED - MORTALITY 44%

1929 - 1938

14/44 PATIENTS DIED - MORTALITY 32%

1939 - 1947

21 OPERATIVE REDUCTIONS

5 DIED - MORTALITY 24%

27 ENEMA REDUCTIONS - MORTALITY 0

1939 - 1947

COMBINED MORTALITY 10%

to the intussusception, which it outlines, producing a concave meniscus. The ends of the meniscus extend proximally until suddenly the intussusceptum gives ground. The meniscus flattens out, then begins to deepen again, and so on. This may take place very quickly. An intussusception protruding from the anus was on one occasion reduced almost too quickly to be followed fluoroscopically. At other times there is a stubborn hang at one level or another and then sudden progress. At times a bubble of air precedes the barium column and alters the fluoroscopic picture. The chief difficulty may be in deciding upon completeness of reduction at the cecum. By displacing the cecum laterally one may see barium well up in the small bowel, and in one of our youngest infants barium went up into the proximal jejunum. If complete reduction is not achieved, the child is permitted to expel the enema and the

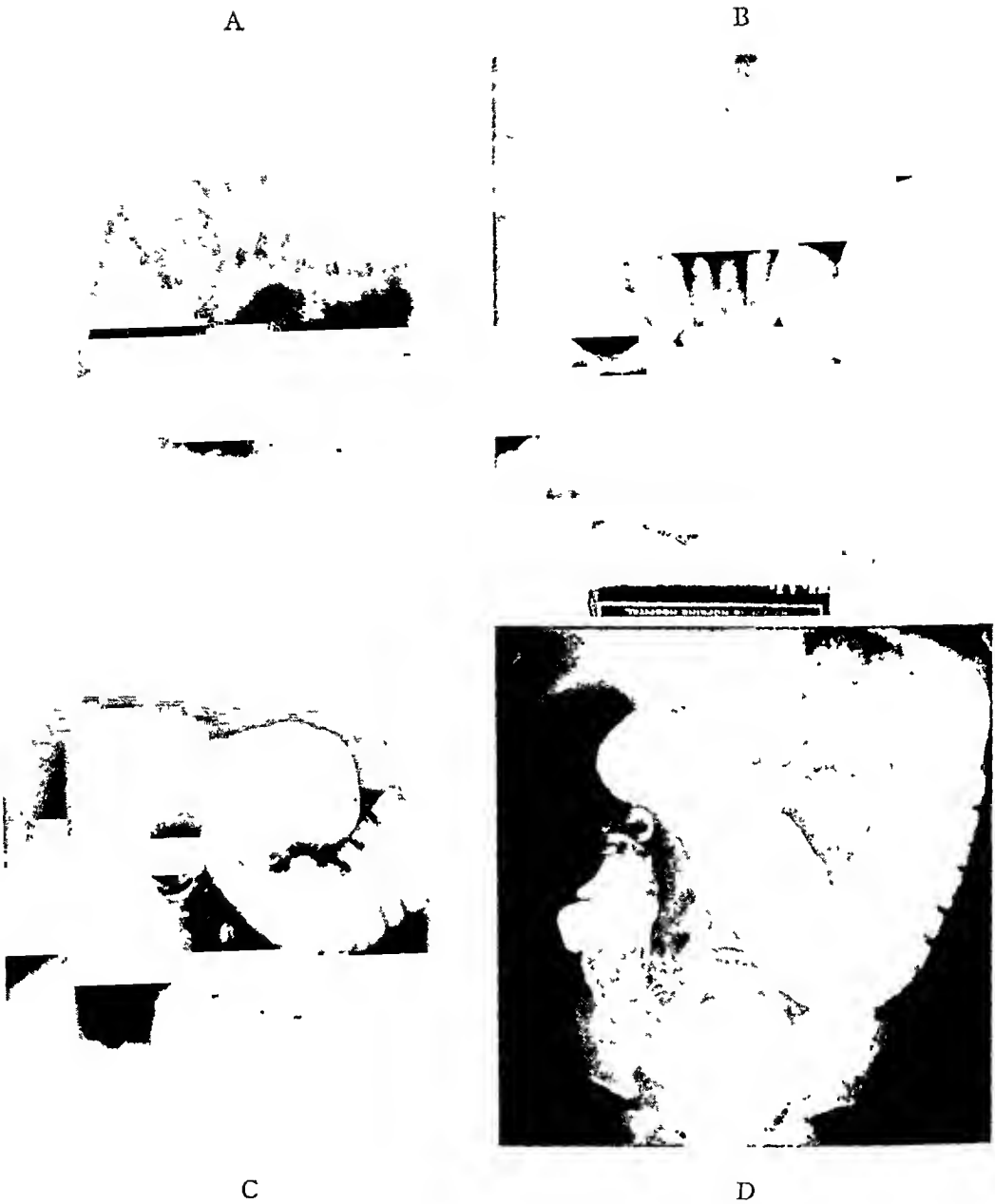


FIG. 1.—Barium enema of an intussusception which has reached the transverse colon.

A. The barium column meets the intussusception and the head of the column shows a concave meniscus.

B. The intussusceptum has been pushed to the hepatic flexure. The barium meniscus extends alongside the intussusceptum.

C. The reduction has proceeded to the ascending colon.

D. The cecum fills irregularly. A mass was still palpable. Through a McBurney incision an annular segment of ileum was pushed back through the ileocecal valve.

effort is repeated. If the third such injection is unsuccessful, operation is performed. After reduction the child is sent to the ward, powdered charcoal is instilled in the stomach and the administration of sulfasuxidine or oral streptomycin is begun as a prophylaxis against enteritis. Six hours later an enema is given to recover the charcoal. A successful reduction is denoted by the following criteria: (1) The entrance of barium well into the small bowel. (2) At times the child returns the barium with feces or flatus, proof in acute intussusceptions that the obstruction has been relieved. (3) The mass is no longer palpable. (4) The child is clinically relieved, often falling off to sleep.

## Position of Intussusceptum

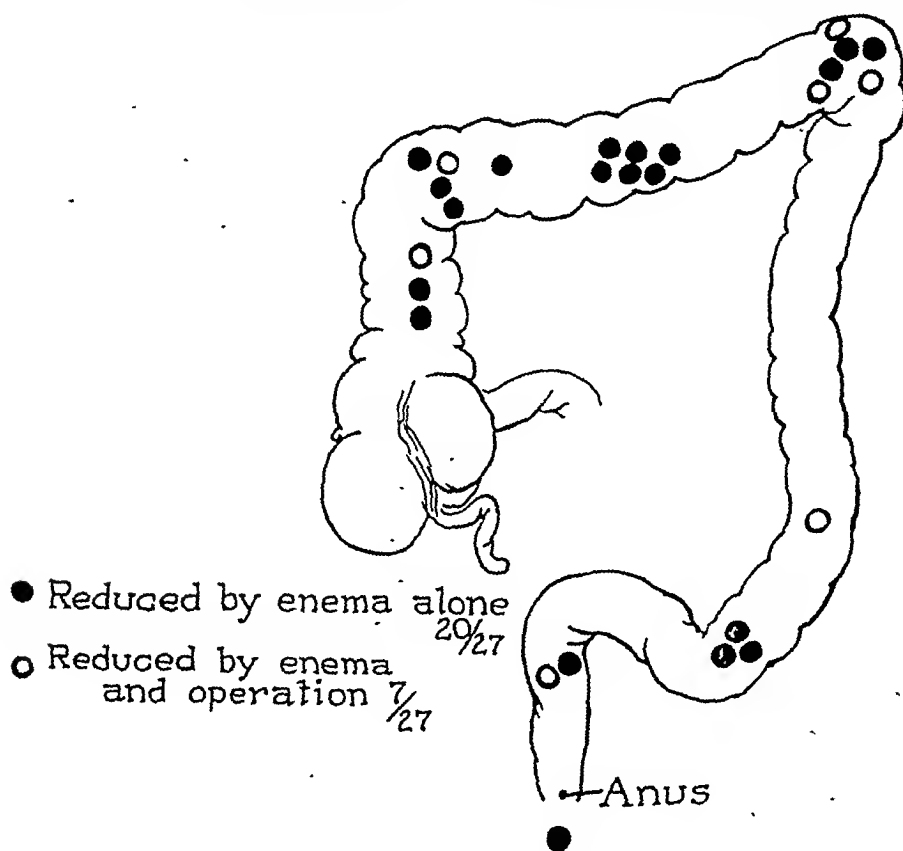


FIG. 2.—In three of the successful reductions by barium enema alone the intussusceptum had reached the sigmoid, in one it had reached the rectum, and in another had prolapsed through the anus. All of those patients requiring operative completion of the reduction were found to have had their intussusception reduced to the cecum or ileocecal valve.

(5) The subsequent recovery in the stool of charcoal given by mouth or the appearance of a blood-free stool is proof of reduction. Hipsley does not use fluoroscopy at all but depends upon the other criteria plus an additional one, namely, if sufficient fluid is injected, that which passes through the ileocecal valve will not be expelled for some time so that there is, after reduction, a persistent measurable increase in abdominal girth.

In the present series 27 intussusceptions were treated primarily by barium enema. All 27 patients survived. Twenty had complete reduction by enema—79 per cent, which is somewhat higher than the figure usually reported. The

diagram (Fig. 2) shows the level which the apex of the intussusceptum had reached when reduction was attempted. It will be seen that complete reduction was secured in a number of patients whose intussusceptions were at the anus, rectum, or sigmoid. Five of the 20 patients whose intussusceptions were reduced by enema alone, were of special interest. In two we were not certain reduction was complete and a McBurney incision was resorted to for verification of the reduction. In one patient, as an experimental procedure, the

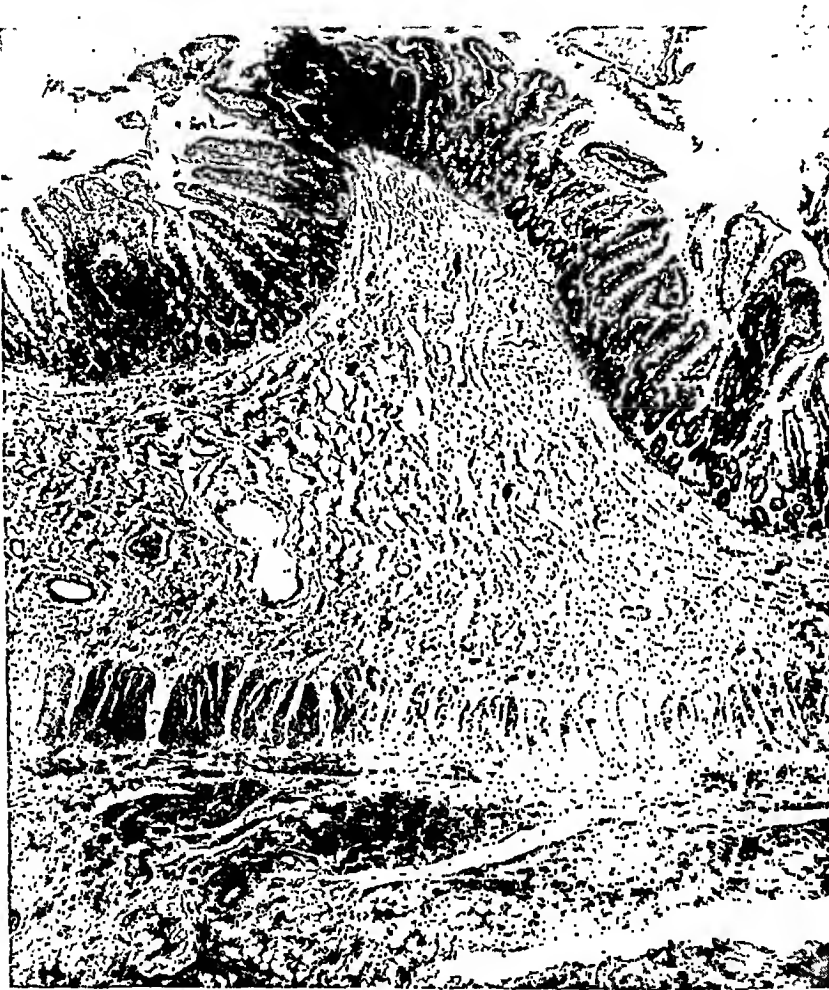


FIG. 3.—Photomicrograph x30 of bowel resected two days after barium enema reduction of intussusception. Child had been having bloody stools after reduction. Thickened bowel was found, thought to be involved in a neoplastic process, and resected. Section shows some sloughing of the tips of villi, massive submucosal edema, subserosal edema, and hemorrhage. Similar changes are regularly seen in animals after reduction of viable bowel.

abdomen was opened, the intussusception in the descending colon brought into view, and then a saline enema administered, reducing the intussusception under direct vision and without manipulation. We were astonished at the swiftness and gentleness of the reduction. A fourth patient had a recurrence two days later, after being symptom free and passing normal stools and the ingested charcoal. Another enema now reduced the intussusception to the cecum, and

exploration showed the appendix still intussuscepted. The appendix was removed and the patient recovered uneventfully. The fifth patient was operated upon 48 hours after enema reduction because of persistent pain, bloody stools, and a palpable right colon. We did not then know that these symptoms are a not rare consequence of reduction by any method. The operator resected the terminal ileum and right colon for great thickening, thought



FIG. 4.—Photomicrograph x60. Section from annular segment of bowel removed at time of operative completion of reduction. The bowel shows early changes of intussusception—loss of epithelium, lymphoid hyperplasia, round cell infiltration in mucosa, submucosal and serosal edema. The bowel was viable.

to be due to tumor. As the photomicrograph (Fig. 3) shows, this was only the edema and organizing hemorrhage which follow reduction. We have reported elsewhere<sup>18</sup> changes much more extreme in the viable bowel of dogs several days after reduction of intussusceptions. It is worth remarking in connection with this patient that diarrhea and even dysentery are not rare occurrences after any type of reduction. Eighteen per cent of our total number of patients had diarrhea after reduction and of six patients who had stool cultures, three had pathogenic organisms.



The seven patients who required operation to complete reduction also survived. In every instance it was found at operation that the intussusception had been reduced to the cecum or ileocecal valve, in five patients from the left colon and in two from the right (Fig. 2). In several instances the operator used a McBurney incision. In only one of these patients had we made a mistaken diagnosis of complete reduction. In him, after a loss of six hours, we then repeated the reduction to the cecum and operation was performed, completing the reduction of an inch of ileum. There was a difference of opinion at the operating table as to whether resection should be performed. The operator did resect an annular segment, section of which (Fig. 4) shows the changes seen early in intussusception when the bowel is viable.<sup>18</sup>

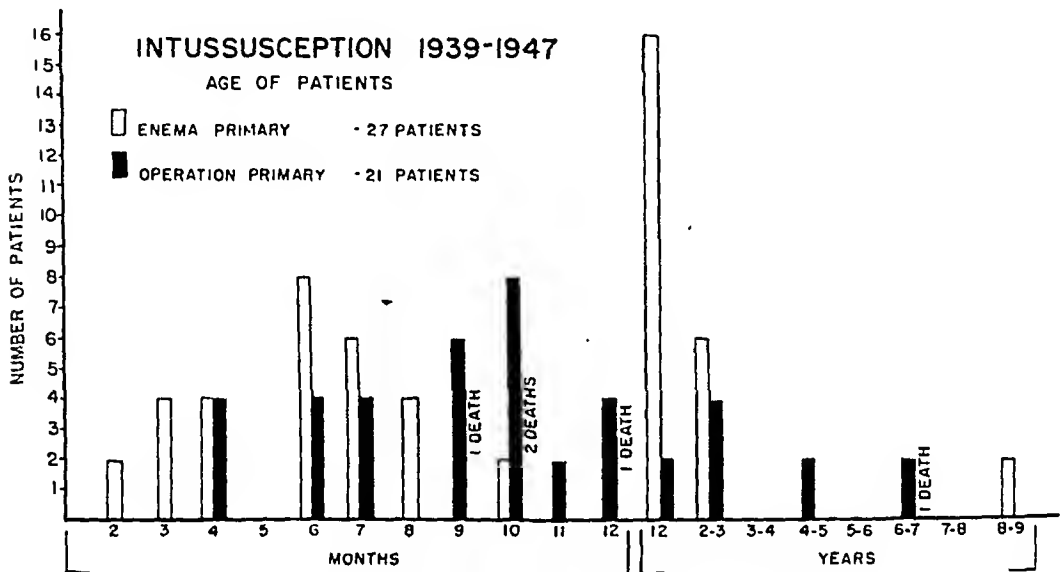


FIG. 5.—There is no marked difference in age distribution of patients in the two groups.

Figure 5 shows the distribution according to age of the patients treated by the two methods. There is no significant difference. Figure 6 shows the distribution according to duration of symptoms of the patients treated by the two methods. The group treated primarily by enema had more of the patients with symptoms of short duration. However, there were four patients in this group with symptoms of over 48 hours' duration.

The point of chief interest in the primary operative group of 21 patients is the history of the five fatal cases. In three the patient was sent home from this hospital the first time he was seen after the onset of symptoms of intussusception. In each instance the child was admitted the next day. Two patients were then operated upon promptly, but with the third there was a delay of an additional 47 hours. A fourth patient was admitted promptly but not brought to operation for 66 hours. All four patients required resection and died relatively soon after operation. A fifth patient was in the hospital, debilitated by polypoid adenomatosis of the entire gastro-intestinal tract, when

his intussusception appeared. Barium enema was not attempted. The child was too enfeebled to withstand his prompt and satisfactory resection and died two days later.

What are the reasons for the resistance among surgeons to a form of treatment which has in so many hands given results superior to those achieved by primary operation? The objections commonly raised are these: (1) The original diagnosis may be uncertain. (2) It is difficult to be sure of reduction. (3) Will not the recurrence rate be higher? (4) Polyps and other tumors cause many intussusceptions and will not be found. (5) In the unsuccessful cases a dangerous delay will have been caused. (6) The bowel may rupture. (7) Nonviable bowel may be reduced.

To answer these objections briefly: (1) As to being sure that one is dealing with intussusception, the diagnosis by fluoroscopy is fairly simple, the criteria are characteristic, and expertness in their recognition is soon acquired. Most cases of intussusception are diagnosed clinically, but a few require barium enema for definitive diagnosis. A good many intussusceptions have been inadvertently reduced in the course of what was meant to be a purely diagnostic barium enema.

(2) Accuracy of diagnosis of complete reduction is high. We have made an erroneous diagnosis of complete reduction once in 27 treatments. If there is any doubt, all that is required is a momentary inspection of the cecum and terminal ileum through a McBurney incision. Even if we were to insist on operative confirmation of every enema reduction, the procedure would still be safer and easier than operative reduction alone. With or without operation the use of hydrostatic pressure is safer and quicker than manual pulling and hauling. (3) As to the rate of recurrence, it is about 2 per cent in patients after reduction by either method. We have had one recurrence in each group in the past ten years. If there is a recurrence, the intussusception should be reduced by enema and the abdomen then explored with the expectation of finding a polyp or other causative lesion. (4) As concerns the possibility of failing to discover such a tumor by barium enema alone, the incidence of tumor is only 2.5 per cent in children under two years who suffer 70 to 90 per cent of the intussusceptions. Furthermore, the tumors which cause intussusception are rarely dangerous in themselves. Table IV shows our experience with such lesions—five polyps, two Meckel's diverticula, and one focus of ectopic pancreatic tissue. (5) As for the delay which may be caused by an unsuccessful attempt at reduction by enema, it requires less than

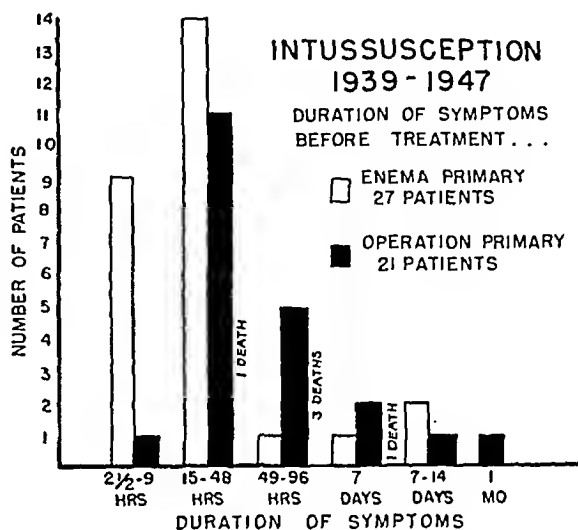


FIG. 6.—There are more patients with symptoms of short duration in the group treated by enema, but four patients in that group had symptoms of over 48 hours' duration.

half an hour from start to finish to reduce an intussusception by this means. At night it is our practice to call the operating room as soon as we make the diagnosis. We usually have finished the reduction in time to cancel the operation before preparations in the operating room have been completed.

We should like to emphasize one point, that this method is not a substitute for surgery, or an escape from surgery. It is as much a surgical procedure as is reduction of a fracture by traction. The surgeon should be as ready to perform a laparotomy, if it proves necessary, as the orthopedist is to perform an open reduction. The treatment should be carried out by a surgeon and in a hospital. It is not an office procedure nor a kitchen table remedy.

As for the next objection, rupture of the bowel, this can occur with hydrostatic pressure as well as with manual reduction during operation. However, it is much less likely to occur with enema since less force is

TABLE IV.—*Demonstrated causes of intussusception in 144 cases of intussusception in infants and children treated at the Johns Hopkins Hospital from 1889 to 1947.*

DEMONSTRABLE CAUSES IN 144 CASES OF INTUSSUSCEPTION			
Cause	Patient's Age	Type (anatomic)	Acute or Chronic
Polyp	11 yrs.	Jejunal	Chronic, recurrent
Polyp	5 yrs.	2 ileal (1 compound)	Chronic, recurrent
Polyp	6½ mos.	No data	Chronic, recurrent
Polyp	1 yr., 2 mos.	Ileal	Acute
Polyp	1 yr., 6 mos.	Ileal	Acute
Meckel's diverticulum	2 yrs, 1 mo.	Ileo-colic	Acute
Meckel's diverticulum	1 yr., 2 wks.	Ileal-ileocaecal (compound)	Acute
Ectopic pancreatic tissue	10 mos.	Ileal	Acute

employed and that force is diffusely distributed. We employ three feet of pressure and never manipulate the bowel. There have been a few instances in Scandinavia of rupture from manual reduction through the intact abdominal wall with or without enema. Mortimer<sup>19</sup> in 1891 tested the resistance of the colon in fresh cadavers to fluid injected under pressure after the ileocecal valve had been ligated. He found serosal cracking beginning occasionally at five feet of pressure, and usually present at eight feet. The bowel sometimes ruptured at six feet of pressure, but more often at higher pressures. In this connection it may be amusing to recall the advice of Forest<sup>20</sup> in the New York Medical Record of 1889, that in reducing intussusception with enema one should "lay the child in the hallway and mount the stairs" holding the fluid reservoir, although he does say that after mounting to a height of 10 feet one should exercise caution!<sup>17</sup> As for reducing nonviable bowel, it would appear that with a pressure of three feet one cannot reduce gangrenous bowel. Our experiments indicate, as others have maintained, that irreducibility of an intussusception is determined by adhesions between the sheaths and by the degree of edema. Both factors increase with time and become more effective in preventing reduction as the damage to the bowel increases.

Table V summarizes our experience in 28 dogs in which intussusception was produced by a method described elsewhere.<sup>18</sup> After periods of observation of 18, 28, 38, and 48 hours the dogs were again operated upon under ether anesthesia, the serosa of the undisturbed intussusception was cultured, and an attempt was made to reduce the intussusception by saline enema under direct vision with just three feet of pressure. It will be seen that reduction by enema was attempted in 28 dogs. In no case did the bowel rupture. In no case did abscess, peritonitis, or any other possible consequence of the reduction of nonviable bowel develop in any animal with a reduced intussusception. The experiments support the clinical observation that one is unlikely to reduce gangrenous bowel by a hydrostatic pressure of three feet. In several instances in another group of animals it was possible to reduce manually invaginations which could not be reduced by hydrostatic pressure.

TABLE V.—*Experimental results. Intussusceptions reduced by hydrostatic pressure at stated intervals after production. No perforation, no reduction of nonviable bowel. Pathogenic bacteria often present on serosal surfaces.*

Duration of Intussusception	Number of Dogs	Result of Enema	Fate of Dog	Peritoneal Cultures
18 hours	4	All reduced	1 anesthetic death 3 survived	3 sterile 1 positive
28 hours	3	All reduced	All survived	2 sterile 1 positive
38 hours	6	All reduced	All survived	1 sterile 5 positive
48 hours	15	2 spontaneously reduced 1 reduced with enema 12 irreducible	2 survived Survived 2 anesthetic deaths 1 survived 8 died 1 sacrificed	2 sterile 8 positive

A few other interesting points are brought out by the study. In 7 out of 13 instances it was possible to culture pathogenic bacteria—*escherichia coli*, *clostridium welchii*, *streptococcus fecalis*, and others—from the serosal surface of viable intussuscepted bowel. This fact may well explain the high fever seen in patients after operation, and the frequency of wound infection and of post-operative adhesions.

Pathologic study of the experimental intussusceptions brought out a number of points of interest. Necrosis begins at the very tip of the intussusception and extends along the outside of the intussusceptum on the returning limb. The microscopic changes are successively those of vascular engorgement of the villi, edema of the submucosa and subserosa, hemorrhage, and finally gangrene. The inner circular muscle coat succumbs sooner than the outer longitudinal muscle coat.

In summary: The cumulative experience of 75 years in the treatment of intussusception shows reduction by hydrostatic pressure to be a safer primary

approach than operation. This conclusion is supported by our clinical and experimental observations. In 27 patients treated primarily by barium enema there were no deaths. The morbidity and length of hospital stay were much reduced when compared with those of patients treated primarily by operation during the same period. The use of hydrostatic pressure under fluoroscopic control in the treatment of intussusception is auxiliary to surgery and not in opposition to it.

*Author's Note:* Since this paper was submitted for publication 6 additional children with intussusception have been treated by barium enema reduction, with no deaths. In 3 enema alone sufficed, in 3 a McBurney incision was required to complete reduction at the ileocecal valve. There is thus a total of 33 cases of intussusception treated primarily by barium enema, with no deaths, 24 of the number being reduced by the barium enema alone.

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# PRIMARY "INFLAMMATORY" CARCINOMA OF THE BREAST\*

## A Report of Five Cases and a Review of the Literature

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THE BREAST is the site of a number of varied pathologic lesions, but none more interesting than "Inflammatory Carcinoma of the Breast," so named because clinically the breast presents signs commonly associated with inflammation.

Frequently these skin manifestations are misdiagnosed and treated as a dermatological or inflammatory lesion rather than as a neoplasm. Four patients with inflammatory carcinoma treated on the general surgical service of the State University of Iowa Hospitals in the last year had been treated as having acute inflammatory lesions prior to admission. To create awareness of this unusual type of neoplasm, and thus prevent loss of valuable time in the institution of therapy at the onset of the disease, available information pertaining to "inflammatory carcinoma" is presented. The material has been obtained from a review of the literature and from personal observation of five patients treated for inflammatory carcinoma at this hospital during the past year.

Two clinical varieties of inflammatory carcinoma of the breast exist. In one group designated as primary, the inflammatory signs arise simultaneously with the carcinoma in the skin of a previously normal breast. It is to be emphasized that in this group there is usually no mass present in the breast, the absence of which frequently accounts for the delay in the correct diagnosis. In the group designated as secondary, the inflammatory manifestations may appear suddenly in a breast which has long been the seat of a scirrhous carcinoma, or in the mate of such a breast or it may follow mastectomy for carcinoma either at the original site, or in the opposite breast. The clinical course and behavior of both types is very much the same. This paper is confined to a discussion of primary inflammatory carcinoma.

Inflammatory carcinoma of the breast presents definite clinical and pathologic characteristics. It is an unusual type of malignancy in that in the early stages it presents signs and symptoms usually associated with acute or sub-acute inflammation. It is a type of neoplasm which presents a rapid rate of spread with early metastasis, and a discouraging response to all forms of treatment.

### HISTORICAL

Probably the first description of this type of mammary carcinoma was by Volkmann<sup>20</sup> in 1875, who called it "Mastitis Carcinomatosa." Since then this neoplasm has received a variety of names, such as Carcinoma erysipeloides,<sup>4, 16</sup> erysipelas carcinomatosa,<sup>10</sup> telangiectatis carcinoma,<sup>21</sup> malignant lymphangitis,<sup>5</sup> and acute carcinoma,<sup>9</sup> usually depending upon the author's interpretation of the signs, symptoms and pathological characteristics. The designation of

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"Inflammatory Carcinoma" was first suggested by Lee and Tannenbaum<sup>11</sup> in 1924 in a report of 28 cases. This terminology has also been used by Taylor and Meltzer<sup>19</sup> who in 1938 presented 38 cases, and by Fox.<sup>8, 9</sup>

Because of the clinical characteristics presented by this neoplasm the nomenclature most favored is "Inflammatory Carcinoma."

#### INCIDENCE

Fortunately this neoplasm is infrequent in occurrence, representing but 1.3 per cent of all cases of mammary cancer, according to Lee and Tannenbaum,<sup>17</sup> Taylor and Meltzer,<sup>19</sup> give a somewhat higher figure of 4 per cent. At the University of Iowa Hospitals five patients with inflammatory carcinoma have been treated in the past 12 months and have constituted 4.2 per cent of malignant breast lesions seen during that period.

The age incidence of inflammatory carcinoma parallels that of breast carcinoma in general. In the 28 cases reported by Lee and Tannenbaum<sup>17</sup> the average age was somewhat younger, being 44.5 years. Ten of the cases, or 39 per cent, occurred in women under 40 years of age. The youngest patient reported with inflammatory carcinoma was 24 years old. Five cases treated at this hospital presented an average of 56 years.

#### PATHOLOGY

Early workers, impressed by the gross inflammatory signs, tried to read inflammatory features into the microscopic picture of the disease. Schumann<sup>18</sup> in 1911 attributed a "toxin-forming power to the carcinoma cells which by setting up a violent irritation, produces a round-cell infiltration closely simulating a primary mastitis."

Learmonth<sup>13</sup> also was of this opinion when he said: "We have to deal with a highly virulent type of cancer cell which is capable of engendering a marked inflammatory reaction."

As early as 1889 Bryant<sup>3</sup> understood that the inflammatory signs of this clinical form of breast carcinoma were due to extensive lymphatic invasion by cancer cells producing edema and capillary congestion. Some early investigators held that the tumor spread was chiefly through the subepidermal capillaries and venules. Ewing<sup>6</sup> advanced the opinion, currently shared by Case<sup>5</sup> and others, that the disease was primarily a continuous growth of carcinoma through the lymphatic vessels.

Because of uncertainty as to whether the vessels by which the tumor cells spread were lymphatics or capillaries, Camiel and Bolder<sup>4</sup> studied approximately 200 serial sections of biopsy material. Barring artefaction the authors presumed the presence of an erythrocyte in a vessel might be taken as evidence of a capillary or venule. None were found.

Using this same criterion, skin biopsies taken from breasts of four of the patients with inflammatory carcinomas treated at the State University of Iowa Hospitals showed many red blood cells in the vessels which contained tumor cells. This is illustrated in the photomicrograph shown in Figure 1. It seems reasonable that spread of the tumor cells may be either by the lymphatics or



capillaries; the disease being primarily a continuous growth of carcinoma through the lymphatic vessels with concomitant blood vessel invasion and congestion of the subpapillary capillaries and venous plexus.

It should be emphasized that true inflammation does not exist. There is no body reaction to an irritant, but the extensive lymphatic blockage causes edema.



FIG. 1.—Photomicrograph showing evidence of spread of inflammatory carcinoma by blood vessels. Note erythrocytes in vascular space with neoplastic cells.

and the capillary congestion produces marked reddening and heat. The round cell infiltration often noted is also due to blockage of lymphatics,<sup>12</sup> and not to an inflammatory reaction.

The histologic type is usually an undifferentiated carcinoma. Microscopic study shows nests of neoplastic epithelial cells in the corium. The neoplastic cells are usually collected in the vascular spaces, lymphatics or both. The spread of the carcinoma is subdermal rather than intradermal, an important

differential point from Paget's disease which involves primarily the epidermis. (Fig. 1.)

#### CLINICAL SYMPTOMS

In the majority of instances the initial symptoms are subjective in nature. The patient will complain of heaviness or aching of the breast. The pain will vary from a dull ache to an intermittent shooting pain.

The patient next notices skin discoloration which varies from bright red to purple and which varies in size and shape. At this time an increase in the size of the breast is also noted. If the patient consults a physician at this stage of the disease the clinical picture closely resembles an acute inflammatory process and is usually treated as such. Of the five patients treated at the University of Iowa Hospitals in the last year, four had received treatment for acute mastitis before being referred for treatment. In the cases reported by Lee, over one-half had been operated upon with a diagnosis of chronic or subacute abscess.

A great amount of valuable time is lost when the neoplasm is treated as an acute inflammatory process. Reuter and Nomland<sup>17</sup> recommend that inflammatory signs developing in the skin or about the breast which do not subside within two or three weeks warrant an incisional biopsy for diagnosis. This is sound advice and if followed it will prevent unnecessary delay in the patient receiving prompt treatment.

Coincident with color change there is an increase in the size of the breast. The involved breast is usually two or three times the size of the normal breast. Patients with inflammatory carcinoma also complain of weakness, easy fatigability, and weight loss, symptoms which may be associated with any malignancy or chronic illness.

As a general rule the patients do not present an elevation of temperature. There are no constant findings in the microscopic examination of the blood. Leucocytosis is the exception rather than the rule. A secondary anemia may be present.

#### CLINICAL SIGNS

Examination of the involved breast in the early stage shows areas of skin discoloration. The color is usually red or reddish purple, but occasionally may be reddish brown in appearance. This discoloration may be seen as irregular patches, or as streaking, the latter resembling lymphangitis in appearance. As the disease progresses the skin becomes deep red or reddish purple in color and begins to extend beyond the confines of the breast. The skin becomes pitted and edematous, and there is pronounced induration of the skin. At this stage the skin shows the "orange peel" or "pitted" appearance. In some cases nipple retraction is present.

The involved breast may be enlarged two or three times the size of the other breast. At the outermost area where involved skin and normal skin merge there is an irregular raised periphery and the appearance is very similar to an acute inflammatory lesion such as erysipelas.

A



B



FIG. 2(A)—Left breast showing irregular erythematous skin discoloration in early stage of primary inflammatory carcinoma. Note resemblance to acute lymphangitis. (B)—Patient shown in 2A after intensive preoperative Roentgen therapy and radical mastectomy. Note diffuse spread of lesion and the erysipelas-like border at the periphery.

The skin is warm to touch and not infrequently tender. Usually a palpable mass is not present.

The gross appearance of inflammatory carcinoma of the breast and the rapid progression of this disease is well illustrated by Figures 2, 3, 4, 5 and 6.

#### DIAGNOSIS

In establishing a diagnosis the following diseases must be differentiated from primary inflammatory carcinoma:

*True inflammation.* As previously mentioned a major difficulty in the diagnosis of inflammatory breast cancer exists in the fact that in its early stages the disease may closely resemble a true inflammatory process of the mammary gland, such as an abscess or an acute mastitis. The skin overlying an abscess of the breast is apt to be smooth, shiny, and tender. Leucocytosis, fever, and other general signs are usually present. Inflammatory carcinoma is typically nontender, covered with edematous "orange peel" skin and unassociated with systemic fever or leukocytosis. An induration in the breast due to lactation mastitis should show in a few days either evidence of resolution or the clinical appearance of abscess. Any case of supposed mastitis persisting longer than two weeks calls for the provisional diagnosis of cancer and warrants incisional biopsy.

*Erysipelas.* The differential diagnosis between erysipelas and inflammatory carcinoma may be impossible on the basis of gross appearance. However, in this region erysipelas is rather uncommon. The disease is quite acute and prostration is usually striking. High fever and marked leucocytosis are present. The lesion is vivid red, disappears on pressure and is not particularly sensitive. The acute history, with the constitutional reaction and dramatic spread of the lesion, together with the decided increase in leucocyte count is sufficient to distinguish erysipelas from inflammatory carcinoma.

*Paget's disease of the nipple.* The skin lesion in Paget's disease involves the nipple, areola, and surrounding skin and presents a reddened, granular surface discharging a yellow viscid fluid. At times the appearance is that of chronic eczema with encrustations. The lesion is frequently confined to the areola alone and the nipple disappears as the disease progresses. In inflammatory carcinoma the nipple is usually not involved other than showing evidence of retraction. There is more diffuse discoloration extending out from the nipple. Biopsy of the involved skin is of value in the final differentiation. The spread of Paget's disease is intradermal, while inflammatory carcinoma is subdermal. Typical signet ring cells known as "Paget Cells" are also seen.

*Plasma cell mastitis.* In the acute phase of plasma cell mastitis the signs and symptoms of a diffuse inflammation radiating from the nipple are seen. However, it varies from inflammatory carcinoma in that the inflammation will subside in from a few days to a week. After subsidence of the acute manifestations a firm irregular tumor remains. With inflammatory carcinoma, as has been mentioned previously, there is usually no mass palpable. Histologic examination of the skin in plasma cell mastitis shows absence of carcinoma,

A



B

FIG. 3(A)—Breast showing skin discoloration and enlargement of primary inflammatory carcinoma. Note small area of involvement on opposite breast. (B)—Patient shown in 3B after intensive Roentgen therapy which had no effect in preventing progression of lesion.

and examination of the mass itself shows the typical picture of plasma cell mastitis as described by Parsons, Henthorne, and Clark.<sup>14</sup>

*Tuberculosis of the breast.* In this condition the onset is less acute. A tumor is present in the breast which is soft in consistency. Early in the course, redness of the overlying skin appears and later areas of softening. As the process extends the skin over the softer portions thins out and finally sinuses form which are usually multiple. Physical signs of tuberculosis elsewhere may also be demonstrated. This condition, from its chronicity and physical signs, may be readily distinguished from inflammatory carcinoma.

*Lymphoma.* Hodgkins disease can produce a picture indistinguishable from inflammatory carcinoma of the breast. The mechanism is undoubtedly a similar one, with acute diffuse lymphatic blockage by multiplying malignant cells. Biopsy is necessary to establish the diagnosis.

*Metastasis.* It has been previously mentioned that the local lesions of inflammatory carcinoma spread with striking rapidity. Metastasis also occurs early in primary inflammatory carcinoma of the breast, involving, in practically all cases, the axillary or supraclavicular nodes. Taylor and Meltzer presented 25 cases of primary carcinoma. In 11 of the 25 cases medical advice was sought within three months of the onset of symptoms, seven saw a physician within six months, and all but one within a year. All 25 cases showed axillary involvement, and nine cases in addition showed clinical evidence of visceral metastases (liver or lung) or bone metastases at the time of examination. At the University of Iowa Hospitals the five cases described below presented themselves for treatment at three months, five months, nine months, 18 months, and 12 months respectively. Four of the five patients presented axillary metastasis. Two in addition evidenced supraclavicular metastases. Liver metastasis was present in one patient. The opposite breast is also frequently involved.

*Treatment.* Whatever the form of therapy the outlook for the patient with inflammatory carcinoma is discouraging. As far back as 1814 Bell<sup>1</sup> appreciated the gravity of these inflammatory signs when in a discussion of carcinoma of the breast he said "When a purple color is on the skin of the tumor, it is a very impropitious beginning."

Portmann,<sup>15</sup> after an extensive review of the treatment of breast carcinoma, stated that brawny red induration and inflammation of the skin, and edema as evidenced by orange peel skin were to be considered as criteria of incurability. Both of these are present in inflammatory carcinoma. Metastasis takes place very early in the disease. In addition the histologic type reveals the carcinoma to be highly malignant. For these reasons the response in the majority of cases to the usual forms of treatment, namely Roentgen-rays, surgery or a combination of the two, has been uniformly bad.

Taylor and Meltzer report 19 cases treated by Roentgen-rays. Three patients were still alive at the end of six, ten and twenty-five months. Nineteen patients lived two to nineteen months after institution of treatment with an average duration of life of 9.2 months.

A



B

FIG. 4(A)—Left breast showing the early skin changes and enlargement of primary inflammatory carcinoma. (B)—Patient shown in 4A after intensive Roentgen and testosterone therapy. Acne and hirsutism due to the testosterone.

Learmonth,<sup>13</sup> reports one patient, treated by surgery, alive after seven years. Brackertz,<sup>2</sup> recommended surgical excision, allowing a 10cm. margin to every trace of redness. Lee and Tannebaum report six patients treated by surgery who had an average duration of life of one year and nine months. Their patients all did poorly, developing prompt evidence of axillary or supraclavicular disease, skin recurrence or involvement of the opposite breast. Fox,<sup>8, 9</sup> reported uniformly bad results with operative treatment.

The present series of five cases illustrates the difficulties presented in arriving at a definite conclusion as to the most suitable type of treatment.

**Case 1.**—A 61-year-old white female complained of aching of the left breast with accompanying discoloration of the skin of three months duration. During this time the patient had received treatment for acute mastitis.

Physical examination revealed the right breast to be two times the size of the left breast. The skin of the breast showed an irregular reddish-purple discoloration. Metastatic nodes were present in the right axilla and supraclavicular regions. Biopsy of the skin was reported as undifferentiated carcinoma. Because of metastases, roentgen therapy was chosen as the method of treatment. This, however, was of no apparent benefit, and the lesion showed a steady progress in severity involving the skin of the back, abdomen, and opposite breast. This patient at last report was rapidly losing ground, 13 months after the onset of her disease.

**Case 2.**—A 58-year old white female complained of a "red, itchy, sore left breast" of nine months duration. During this time the patient had been treated for acute mastitis.

Physical examination revealed the left breast to be enlarged one and one-half times that of the right breast. The skin of the breast was indurated and several irregular erythematous areas were present. Axillary metastasis was present.

The patient received an intensive preoperative course of roentgen therapy. Examination two months later showed definite regression of the lesion, so much so that a radical mastectomy was performed. Histologic examination of the lesion was reported as poorly differentiated carcinoma. This patient did extremely well for approximately nine months after discharge from the hospital. At this time she developed a purpuric lesion of the anterior and lateral chest wall. She was treated by her local physician for herpes zoster. When the patient returned to this hospital for examination, biopsy revealed the lesion to be carcinoma. Testosterone as a palliative resort was started within the last week; evaluation of the treatment cannot therefore be made at this time.

This patient of the five patients presented had shown the best response to treatment having been free of evidence of carcinoma approximately one year. However, with evidence of recurrence of the carcinoma now present it illustrates the discouraging response of inflammatory carcinoma to available therapy.

**Case 3.**—A 58-year-old white female complaining of enlargement and irregular erythematous discoloration of the left breast of one years' duration. Physical examination revealed the left breast to be two to three times the size of the right breast. There was a diffuse erythematous discoloration and lymph-edema of the breast. Nipple retraction was present. A metastatic node was palpable in the left axilla.

The same type of therapy was decided upon as was given in Case 2. The patient received an intensive course of roentgen therapy. The patient returned in two months for radical mastectomy. Examination revealed an irregularity of the right tenth rib anteriorly. To rule out a metastatic lesion this area was explored. This revealed a fracture of the tenth rib at the costo-chondral junction which accounted for the irregularity palpated. Through this incision the liver was felt through the peritoneum and found to be nodular. A small incision was made through the peritoneum and many metastatic nodules were found. Biopsy revealed the presence of carcinoma. Testosterone



FIG. 5



FIG. 6

FIG. 5—Left breast showing characteristic enlargement that occurs in primary inflammatory carcinoma.

FIG. 6.—Right breast and surrounding skin showing marked involvement with primary inflammatory carcinoma. This patient had received intensive Roentgen therapy.

therapy was instituted without benefit. The patient died several months after discharge from the hospital approximately 19 months after onset of symptoms.

**Case 5.**—A 55-year-old white female complaining of soreness and skin discoloration of the left breast of five months duration.

Physical examination revealed the left breast to be enlarged two times that of the right breast. The skin of the breast was diffusely reddened and indurated. Axillary and supraclavicular node metastases were present. Biopsy of the skin and of a supraclavicular node were reported as undifferentiated carcinoma.

The patient was given an intensive course of roentgen therapy. Examination two months later revealed progression of the neoplasm. Testosterone therapy was started. A dosage of 100 mg. daily was prescribed. The patient has returned for examination at intervals of one month for the past eight months. At the completion of two months of therapy there was evidence of regression of the inflammatory signs with an increased feeling of well being experienced by the patient. This improvement continued for an additional three months. At this time examination once again revealed definite evidence of spread of the carcinoma. At the last examination eight months after testosterone therapy was instituted the patient has continued to experience a feeling of well being in spite of progress of the local lesion. It is believed that this patient has received definite benefit from testosterone therapy.

**Case 5.**—A 52-year-old white female admitted with diabetic gangrene of the right foot of four weeks duration. In addition physical examination revealed a markedly enlarged right breast. The skin was brawny reddish purple in color, and indurated, presenting an orange peel appearance. The skin involvement extended to the supraclavicular lesion superiorly, the medial portion of the left breast, the costal margin inferiorly, and the posterior axillary line posteriorly. Skin biopsy revealed poorly differentiated adenocarcinoma.

The patient gave a history of the breast lesion beginning approximately 18 months earlier. It was ignored until two months prior to admission at which time a physician was consulted and an intensive course of roentgen therapy was given. From the appearance of the lesion it appeared to have been benefitted very little by this treatment.

The patient was seen by the Department of Rontgenology who expressed the opinion that further therapy would be of no value. Testosterone therapy was prescribed. The patient died suddenly 11 days after therapy was started and one week after discharge from the hospital. This patient survived 19 months after onset of her symptoms.

The above case histories do not lead to any definite conclusions about the treatment of inflammatory carcinoma other than that the outlook is very discouraging. Three patients have died 13, 19, and 19 months respectively after onset of their disease. Two patients are still alive 19 and 21 months after onset of symptoms. However, continued spread of the carcinoma in these cases, in spite of all available therapy, suggests an apparently hopeless prognosis.

The most favorable result was obtained in Case 2, the patient receiving preoperative roentgen-ray followed by radical mastectomy, although recent examination showed evidence of recurrence. Roentgen-rays alone have proved to be of little benefit in stopping the spread of inflammatory carcinoma, other than showing an initial favorable response in Case 2.

Case 4 is of interest in the systemic improvement experienced by the patient when placed on testosterone therapy. In spite of continued progress of the local lesion the patient continued to experience a feeling of well being and was able to carry on her normal household duties.

In view of the highly malignant nature of this disease, it is recommended that the patient be given every opportunity for cure through a combination of

all therapy available. This would include an intensive course of preoperative roentgen-ray therapy, followed by radical mastectomy in cases deemed operable. The inoperable cases who do not respond favorably to roentgen-ray therapy should be given the benefit of testosterone proprionate. The greatest aid for improvement of therapy would be earlier diagnosis. Recognition of the disease at the onset would allow prompt institution of treatment and perhaps produce a more favorable result.

## SUMMARY

1. Primary inflammatory carcinoma, an interesting, infrequent and highly malignant tumor of the breast has been described.
2. The age incidence parallels that of breast carcinoma in general.
3. The disease is primarily a continuous growth of carcinoma through the lymphatic vessels with concomitant blood vessel invasion.
4. The histologic type is usually undifferentiated carcinoma or poorly differentiated adenocarcinoma.
5. Symptoms are acute in onset, most frequently characterized by enlargement and aching of the breast with concomitant inflammatory signs, and, in the early stages of the disease, resembling an infectious process.
6. Differential diagnosis is made by absence of generalized symptoms indicating an infectious process, normal blood count and biopsy.
7. Metastasis takes place early and in practically all cases the axillary and supraclavicular nodes are involved.
8. Response to treatment is uniformly poor. Roentgen therapy and surgery in the operable cases has been of some value. Roentgen therapy and testosterone proprionate are recommended for the inoperable cases.
9. Biopsy of inflammatory lesions of the breast which persist over two weeks, to aid in early diagnosis and institution of proper therapy, is urged.

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# THE SILENT GALLSTONE: A TEN TO TWENTY YEAR FOLLOW-UP STUDY OF 112 CASES\*

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BECAUSE, SINCE THE ADVENT OF CHOLECYSTOGRAPHY, the problem of the silent gallstone has become an increasingly frequent and, consequently, an increasingly important one, several pertinent questions are being asked. How often are gallstones silent and how often is the physician confronted with the problem of the silent gallstone? What advice should be given the patient who has silent gallstones? Should he be told to undergo cholecystectomy at the first attack of colic or after several attacks have occurred? Should he be told to await development of dyspepsia or colic before submitting to surgical treatment? Should he be urged to undergo cholecystectomy at the first attack of colic or after several attacks have occurred?

## FREQUENCY OF THE SILENT GALLSTONE

The frequency with which the silent gallstone occurs in the general population is not known. Surveys using cholecystography, so far as we are aware, have not been made to determine the incidence. Some idea of its frequency, however, may be gained by consideration of data obtained from necropsy studies. Robertson,<sup>1</sup> in reviewing the records of 1,027 cases in which necropsy was performed and in which gallstones were or had been present, found that in 61 per cent there had been no suspicion by the patient or his attending physician that gallstones did exist. Obviously, given the opportunity of questioning by the physician during the patient's life, not all of the 61 per cent would have been classified as cases of silent gallstones but, after taking into consideration this source of error, it seems that the percentage of silent gallstones may well be high. When these data are considered in relation to the finding of Robertson and Dochat<sup>2</sup> that in 16.3 per cent of 16,926 necropsies gallstones were present and that the proportion ranged from 0.1 per cent in the first decade of life to 32.7 per cent in the ninth decade of life, one is impressed not only with the large number of gallstones but also with the large number of silent gallstones potentially present in the general population.

## PREVIOUS VIEWS ON TREATMENT FOR THE SILENT GALLSTONE

There is widespread agreement that surgical treatment is indicated in the symptomatic or calculous disease of the gallbladder producing distressing dyspepsia or

and when the complications thereof arise, but agreement that silent gallstones require surgical treatment is lacking. This has been true both in the early years and since cholecystography has permitted such a diagnosis frequently. Before 1924, the remarks of Kehr,<sup>3</sup> W. J. Mayo<sup>4</sup> and Osler<sup>5</sup> summarize the several attitudes of the day toward the silent gallstone. In 1901 Kehr stated that "quiet lying gallstones are no subject for treatment, for a persistent latent stage is almost as good as a cure." On the other hand, in 1911, W. J. Mayo said: "Ten years ago we heard a great deal about 'innocent' gallstones which meant that gallstones existed without symptoms and that their presence was not suspected until postmortem examination brought them to light. . . . That temporary palliation can be procured with nonoperative treatment cannot be denied, but the cure of the patient can only be brought about by surgical means." Osler<sup>5</sup> in the following year, 1912, said that surgical treatment of the gallbladder was indicated "after repeated attacks of colic, in the presence of a distended gallbladder associated with attacks of pain or fever, and a stone in the common duct."

Since 1924 and the introduction of cholecystography by Graham and Cole the same variations in attitudes toward treatment of the silent gallstone may be found. White,<sup>6</sup> in 1928, stated that "many silent gallstones show a gallbladder wall that is bacteriologically negative. Cholesterol stones especially lie dormant for years. Surgery should be based on symptoms, not on the mere presence of stones or low grade infection. I believe that most patients escape perceptible injury to other organs." Mason and Blackford<sup>7</sup> said in 1932: "We fear that occasionally surgical relief is advised because of refinements in the interpretation of symptoms together with new methods of diagnosis of gallbladder disease, rather than because of the former clinical symptoms." Musser<sup>8</sup> concluded in 1934 that "it is doubtful if interference is indicated for the first or even the second biliary colic if evidence of infection is lacking." Andrews<sup>9</sup> said in 1936, "I think the operation on silent gallstones is a scandal."

On the other hand, Lahey<sup>10</sup> in 1938 expressed the conviction that there are no harmless gallstones "and that because of the above dangers [acute cholecystitis and biliary obstruction] all gallstones should be removed. It has frequently been urged and practiced that a proper attitude to take toward gallstones is that operation should not be undertaken until they produce symptoms. If one deals with gallstone patients in large numbers one cannot help being impressed with the fact that this philosophy results in many situations and in many fatalities which would not have occurred had the operative procedure been undertaken earlier." Cheever<sup>11</sup> shares Lahey's opinion that "there are no harmless gallstones . . . that cholecystectomy should be advised unless special contraindications exist when the diagnosis of gallstones is made." Carter, Greene and Twiss<sup>12</sup> in 1939 said that "in every instance in which stones can be demonstrated to be present, surgery is indicated to prevent the dangers of acute ulcerative cholecystitis."

Fitz<sup>13</sup> in 1942 expressed the belief that the "most judicious therapy of 'silent' gallstones may be different than in their later stages of symptomatic activity. . . . The very ease with which gallstones can now be recognized

by cholecystography may lead to errors in therapeutic judgment. . . . It is not harmful to follow patients with 'silent gallstones' for a time before advising surgery, and it may be helpful."

It is interesting to compare the views on this problem as stated in "Nelson's new loose-leaf surgery" and "Nelson's new loose-leaf medicine." Whipple,<sup>14</sup> writing in the former, concluded that "if the gallbladder is the seat of definite chronic inflammation and especially if the chronic inflammation is associated with gallstone formation, surgery is the only therapy that offers permanent and satisfactory cure." Writing in the latter, Miller and Machella<sup>15</sup> stated that "opinion is divided as to the propriety of operating in cases of stones in the gallbladder without symptoms and in which the diagnosis is made accidentally. Since such patients have gone through a long life without digestive symptoms, one would seem to be justified at least in postponing surgery until some symptoms develop."

Meakins'<sup>16</sup> stand on this question should be considered. Concerning gallstones, he expressed the belief that "their removal by operation is not indicated for the first, second, or even several attacks of colic. There may be lengthy intervals and the disability of an occasional attack may be relatively insignificant compared to the risk of operation, which is not inconsiderable, particularly in elderly people affected with diabetes, obesity, hypertension, and myocardial degeneration, all or any of which are commonly associated with gallstones." Christian,<sup>17</sup> in Osler's "The Principles and Practice of Medicine," expressed a view similar to that of Meakins: "The decision for or against surgical treatment should be made in the course of repeated attacks; the single attack requires operation only in the unusual case of steadily increasing severity and evidence of severe infection. There are many patients in whom the symptoms are slight, for these surgical treatment is not indicated. . . . It is rare that cholecystectomy is advisable for the first attack, even though it is severe and typical. The present author has long followed the policy just stated; in his patients it has led to no serious consequences that would have been avoided by early cholecystectomy. . . ."

Watson,<sup>18</sup> writing in Cecil's "A Textbook of Medicine," introduced another factor. He wrote, "In the usual case, however, cholecystectomy is indicated because of the many serious complications which gallstones may produce. . . . Furthermore, the important relation of cholelithiasis to the occurrence of primary cancer of the biliary tree must be taken into account."

Finally, the opinion of Clute and Kenney<sup>19</sup> (1944) is that "in the great majority of simple or silent gallstones an early elective cholecystectomy is wiser than an operation into which one is forced by the complications of the disease."

The wide divergence in opinion regarding the treatment of the silent gallstone probably arises from the lack of accurate data pertaining to the incidence of dyspepsia and colic and of the complication of calculous disease of the biliary tract in cases of gallstones which are silent when discovered. Data regarding the incidence of the several complications of calculous disease of the gallbladder in large series of patients coming to operation are available

but these data do not apply to the incidence of the several complications in cases of silent gallstones.

It is doubtful whether carcinoma of the gallbladder should be emphasized as a hazard of silent gallstones adequate to demand surgical intervention for its prevention. Not only is carcinoma of the gallbladder relatively rare but also it appears that this neoplasm is found most frequently when symptoms of cholecystitis have been present for many years. Jaguttis,<sup>20</sup> in 1926, reported that cancer of the gallbladder developed in five of his 114 patients who had had symptoms of cholecystic disease for 10 to 25 years. Vadheim, Gray and Dockerty<sup>21</sup> found that symptoms of disease of the biliary tract had been present in their 77 cases of carcinoma of the gallbladder for an average of 14.2 years in 80 per cent of the patients.

Similarly, the incidence of stone in the common duct appears to be related to the duration of symptoms. In a study by Heyd<sup>22</sup> of 1,270 cases in which symptoms of gallstones had been present for two years or less, the incidence of stones in the common duct was 1.9 per cent. In another group of patients in which the symptoms of cholecystic disease had been present for 10 to 25 years, Heyd found the incidence of stones in the common duct to be 16.0 per cent. So long as the stone remains silent, the chances are that its site in the common duct must be small.

#### DATA OF VALUE IN DETERMINING POLICY ON TREATMENT

To decide for or against surgical treatment of silent gallstone, the physician should have certain information. He should know in how many cases of silent gallstone dyspepsia, and in how many cases colic, appears at a later date. He also should know in how many the complications of calculous disease of the gallbladder develop. Also, it would be of value to know how frequently complications occur with the first attack of colic. Such data would be valuable in establishing the risk to the patient who has silent gallstones of deferring surgical intervention until the first attack of colic, because the mortality of cholecystectomy for uncomplicated disease of the gallbladder is about 0.5 per cent and for complicated disease of the gallbladder, 3 per cent in the hands of an experienced surgeon. These data are needed for evaluation before one is able to decide whether or not a patient who may never have incapacitating dyspepsia, an attack of colic or complications, should undergo a surgical procedure which carries a risk of at least 0.5 per cent.

#### MATERIAL AND METHODS OF STUDY

In the hope of supplying some of the data not now available but necessary for decision regarding treatment of the silent gallstone, a long-term follow-up study of all cases in which gallstones were found incidentally during the course of some other abdominal operation at the Mayo Clinic was carried out. The records of 998 such cases occurring from 1925 through 1934 were reviewed. Approximately a half of these were discarded as unsuitable for long-term follow-up because the operation had been for cancer. Many others, including those with duodenal ulcer, were discarded because some of the abdominal

symptoms might have been due to the cholelithiasis. Follow-up letters were sent to 184 persons. Replies were received from 115 (62 per cent). Each patient was asked if indigestion or colic had preceded the discovery of the gallstones and several replied that symptoms had been present, so that these, too, were discarded. Finally, 112 cases were considered suitable for study. The average age of the 112 patients was 48.2 years when the gallstones were discovered.

#### RESULTS OF STUDY

The first report on the course of the calculous disease of the gallbladder in these 112 patients will be given.

In 30 cases indigestion developed and it is assumed that the indigestion in each case was due to the disease of the gallbladder. Under the term "indigestion" are included those cases in which such symptoms as gaseous indigestion, intolerance to certain foods, and heartburn developed, as the only abdominal distress. The severity of the indigestion varied; some patients were bothered occasionally, a few were able to control all symptoms by diet while others felt that the indigestion was incapacitating.

Twenty-one patients reported colic; more than half had experienced more than one attack of colic, but several who had had frequent and severe attacks of colic found that sooner or later the attacks had subsided so that they had had no symptoms whatsoever for years. Five of the 21 patients had both colic and jaundice; of the five, four had had slight jaundice which followed an attack of colic and was transient only. The fifth patient underwent operation immediately after the first attack of colic and jaundice.

In a total of 51 (45.5 per cent) of the 112 cases symptoms developed. In 24 of these 51 cases cholecystectomy was performed. Three of the 24 patients died postoperatively. The death of the patient who underwent operation at this clinic was due to pulmonary embolism. Of the two who underwent operation elsewhere, one death was reported by the patient's relatives to be due to subphrenic abscess and the other to a "weeping" liver. In 61 (54.5 per cent) of the 112 cases abdominal symptoms did not develop before death or have not developed since the discovery of the gallstones.

It is of interest that 28 of the patients have died. Of the 28, 21 did not, so far as can be ascertained, experience symptoms prior to death but seven did so. The cause of death was unknown in four cases, while death was due to cancer in six, to heart disease in five, to infectious disease in five, to cerebral accident in four, to amputation of the leg in one, and followed cholecystectomy in three. In not one of the six cases in which the patient died of cancer was the gallbladder the seat of the cancer.

#### COMMENT

Although we recognize the limitations of the information obtained by follow-up letters, none the less, this study furnished interesting and thought-provoking data. Although these data do not give conclusive information about the risk of nonoperative and operative treatment of the silent gallstone,



they are noteworthy on this basis: that the patient with silent gallstone may be told that he has about an even chance that symptoms will develop, that he has about one chance out of five that painful seizures will develop and a small chance that jaundice will develop within ten to 20 years. In addition, he should be told that the risk of surgical intervention at the best is about 0.5 per cent when cholecystectomy is performed before complications develop, that the risk will increase to about 3 per cent if he defers surgical intervention until complications develop, or old age and physical debilities appear, but that the increase in risk is counterbalanced by the fact that if he defers surgical intervention he may never require operation. It is not possible on the basis of information now available to tell the patient whether the risk is greater or smaller if operation is performed while the gallstones are silent than if it is postponed until symptoms develop. Certainly, the mortality rate will be low regardless of the choice made.

The reaction of the patient to his problem will be an important determining factor. Many patients will prefer to have gallstones removed in order to eliminate the threat of painful seizures or severe complications. Others, knowing the higher risk of surgical intervention should complications develop, will prefer to take the chance that no symptoms will develop. Surgical treatment of the silent gallstone may be classified as optional or elective surgery, but surgical intervention should not be postponed after symptoms, and more especially after attacks of colic, appear.

#### CONCLUSIONS

Developments over a period of ten to 20 years in 112 cases of silent gallstones have been ascertained. In 61 cases symptoms did not develop. In the 51 cases in which symptoms occurred, 30 patients complained only of dyspepsia and 21 experienced painful seizures. Five of the 21 patients experiencing painful seizures also had jaundice.

Cholecystectomy may be advised but need not be urged, if the patient prefers to accept the chance of experiencing painful seizures or the increased risk of surgical treatment in the event the complication of calculous disease of the biliary tract appears.

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# THORACO-ABDOMINAL APPROACH FOR PORTACAVAL ANASTOMOSIS\*

WITH A CASE REPORT OF PORTACAVAL SHUNT EMPLOYING THIS METHOD

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THE WORK OF BLAKEMORE and Lord,<sup>1</sup> Whipple,<sup>2</sup> and Blakemore,<sup>3</sup> has established portacaval shunt as an effective means of treating portal hypertension in properly chosen cases. The indication for, the results of, and the problems attending this operation have recently been reviewed by Blakemore.<sup>4</sup>

The usual approach for portal vein shunt operations (portacaval or splenorenal), is through a wide transverse or an extensive left paramedian abdominal incision. By means of pressure readings of the various parts of the portal system, one can determine whether a portacaval or splenorenal anastomosis is indicated. In general, if either one can be used, as is the case in the intrahepatic block of cirrhosis of the liver, the portacaval shunt is the more desirable, since it offers a larger shunt.<sup>5</sup> The difficulty with the portacaval procedure, however, lies in the fact that the exposure is hardly adequate, necessitating working in a small area under the costal cage, in a deep wound. For this reason many surgeons have been employing the less efficacious but easier splenorenal shunt in instances of intrahepatic block.

It occurred to the writer that a transthoracic, thoraco-abdominal approach to the hilum of the liver would not only give more direct access to the region and present the structures of the hilum and inferior vena cava more superficially but would permit freer mobilization of the liver by permitting its dislocation into the right thorax through the incised diaphragm. Moreover, by placing the patient in a true lateral position, with the right side up, the relationship of the common duct and hepatic artery to the portal vein could be altered from the surgeon's point of view; the portal vein would now be lying to one side instead of behind the above-named structures, thereby excluding the necessity of dissecting the common duct and hepatic artery in order to reach the portal vein. Finally, because of the better exposure and the freer mobilization of the tissues in this region, it would be possible to dissect out the portal vein beyond its point of bifurcation; the branches of the portal vein could therefore be tied and a greater length of the portal vein be preserved for its anastomosis to the inferior vena cava. Obviously, the added advantage of the greater mobilization of the portal vein lies in the fact that there is less danger of tension at the suture line. Then, too, by ligating the branches of the portal vein, the stump is reduced to a minimum, thereby reducing the possibility of an ascending thrombosis initiating in a blind venous pouch.

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## PORTACAVAL ANASTOMOSIS

With these advantages in view, starting on January 17, 1948, six dogs were subjected to the thoraco-abdominal approach for portacaval anastomosis. In four dogs an incision was made along the course of the ninth rib, from the right lateral margin of the erector spinae muscles to the lateral border of the right rectus muscle. In two dogs the thoraco-abdominal approach was made through the eighth interspace. Either method can be used, depending on the individual surgeon's preference for rib resection or intercostal incision. It



FIG. 1.—The exposure made possible by thoraco-abdominal approach: 1. Finochietto rib spreader between eighth and tenth ribs; 2. Lower lobe of the right lung; 3. Upper leaf of incised diaphragm; 4. Liver. Note marked cirrhosis; 5. Clamp points to lower leaf of severed diaphragm. The wound extends well to the right of area shown in this picture.

may be advisable in some instances to resect the eighth rib, depending on the size of the liver. In each dog the costal cage was opened under positive pressure anesthesia and the diaphragm incised along the line of the wound in the direction of its fibers. The incision was extended through the abdominal muscles to the lateral border of the right rectus muscle, and the peritoneum in this region was opened so as to unite the right hemi-thorax with the abdominal cavity. The intestines were packed away, and the hilum of the liver, the right kidney, the right adrenal gland and the inferior vena cava were easily exposed. The peritoneum over the inferior vena cava was incised and the inferior vena cava was mobilized from the renal vein to the point where it

passed under the liver. The portal vein was then approached; it was clearly discernible to the lateral side of the common duct and hepatic artery. The portal vein was mobilized along its entire length, up to the point where it enters the substance of the liver after branching. It was ligated beyond the point of bifurcation and transfixed by suture-ligature just at the point of bifurcation. The lower portion of the portal vein was compressed by means of a Blalock clamp. A clamp with a deep curve was then placed over the



FIG. 2.—Following retraction, the structures to be dealt with are exposed: 1. Inferior vena cava. Note strands of adventitia not yet dissected away; 2. Liver; 3. Portal vein; 4. Common duct pointed out by clamp.

right superior aspect of the inferior vena cava above the renal vein so that the passage of blood would not be obstructed during the anastomosis. A piece of vein between the clamp was excised so as to prevent closure of the aperture postoperatively. A direct end-to-side anastomosis between the portal vein and the inferior vena cava was successfully carried out in all six dogs by use of an everting suture, as described by Blalock,<sup>6</sup> thereby effecting an intima to intima approximation of the vessels. No. 00000 braided black silk on an atraumatic needle was used.

On January 28, 1948, this technic was employed on a 45-year-old male patient suffering from cirrhosis of the liver; he had experienced four episodes of nearly exsanguinating hemorrhage from rupture of esophageal varices, and at the time of operation exhibited a moderate degree of ascites. The operation



FIG. 3.—Completed posterior layer of anastomosis: 1. Stiles rubber-shod kidney clamp on inferior vena cava; 2. Blalock clamp; 3. Portal vein; 4. A forceps holding away anterior layer of portal vein. Note the intima-to-intima anastomosis of these vessels.

was performed under intratracheal cyclopropane anesthesia, with the patient lying on his left side in the true lateral position, supported by a sand bag under the left loin. The ninth rib was resected subperiosteally from its angle to the costochondral junction. The costochondral junction at this point was

cut through, connecting the right thorax with the abdomen. The diaphragm and the muscles were incised along the line of incision. Bleeders from the edges of the diaphragm were clamped and ligated. The intestines were packed away and, because of the posterior lateral exposure afforded by this approach, the need for resection of adhesions from a previous anterior abdominal operation was completely obviated. An excellent view of the hilum of the liver, the right kidney, and inferior vena cava was obtained. The peritoneum lateral to the inferior vena cava was incised. At this time the right adrenal gland was brought clearly into the field. The inferior vena cava was mobilized and vaselined umbilical tape was passed around it for better control of the vessel. Beginning laterally, so as to avoid injury to the common duct, the portal vein was then mobilized from its origin to beyond the point of its bifurcation. It was possible easily to mobilize the common duct along its entire length, suggesting the value of this approach for difficult hilar reparative surgery of the common duct. The hepatic artery did not come into view during the entire procedure. By means of a Lahey clamp, the right and left branches of the portal vein were dissected out, and double No. 24 cotton ligatures were passed around each. Vaselined umbilical tape was placed around the lower region of the portal vein, and a small tributary to the portal vein near the hilum of the liver was ligated and cut. The portal vein was then placed between the jaws of a Blalock clamp. At this time an attempt was made to take pressure readings of the portal vein but unfortunately the manometer system did not work satisfactorily. The Blalock clamp was then closed and the sutures which had been placed around the branches of the portal vein were tied. A transfixion suture-ligature of No. 24 cotton was then placed in the portal vein at the point of bifurcation. The portal vein was cut transversely between the ligatures and the Blalock clamp which had been placed well away from the transfixion ligature. By using the handle of the clamp for traction, mobilization of the portal vein circumferentially was easily performed down to the origin of the vessel. A Stille's rubber-shod kidney clamp was then placed on the inferior vena cava above the renals, as described in the discussion of the animal work.\*

An incision was made longitudinally into the inferior vena cava for about 3 cm., corresponding to the width of the severed portal vein. A portion of the inferior vena cava was excised along the line of incision (approximately 2 mm. in the center and 1 mm. at the ends),\* so as to preclude the possibility of postoperative spontaneous closure. The site selected for anastomosis insured against any possibility of angulation. A direct-end-to-side intima-to-intima anastomosis between the portal vein and inferior vena cava was then established by means of a running everting mattress suture. The suture was tied on the outside at one end and continued across the posterior layer to the opposite margin where a knot was again tied on the outside. These knots prevent pursestringing of the suture line. The anterior layer was likewise

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\* A special vena cava clamp and a curved long-handled scissor for excising a portion of the vein have since been devised. (They are manufactured by George P. Pilling and Son Company, Phila., Pa.)

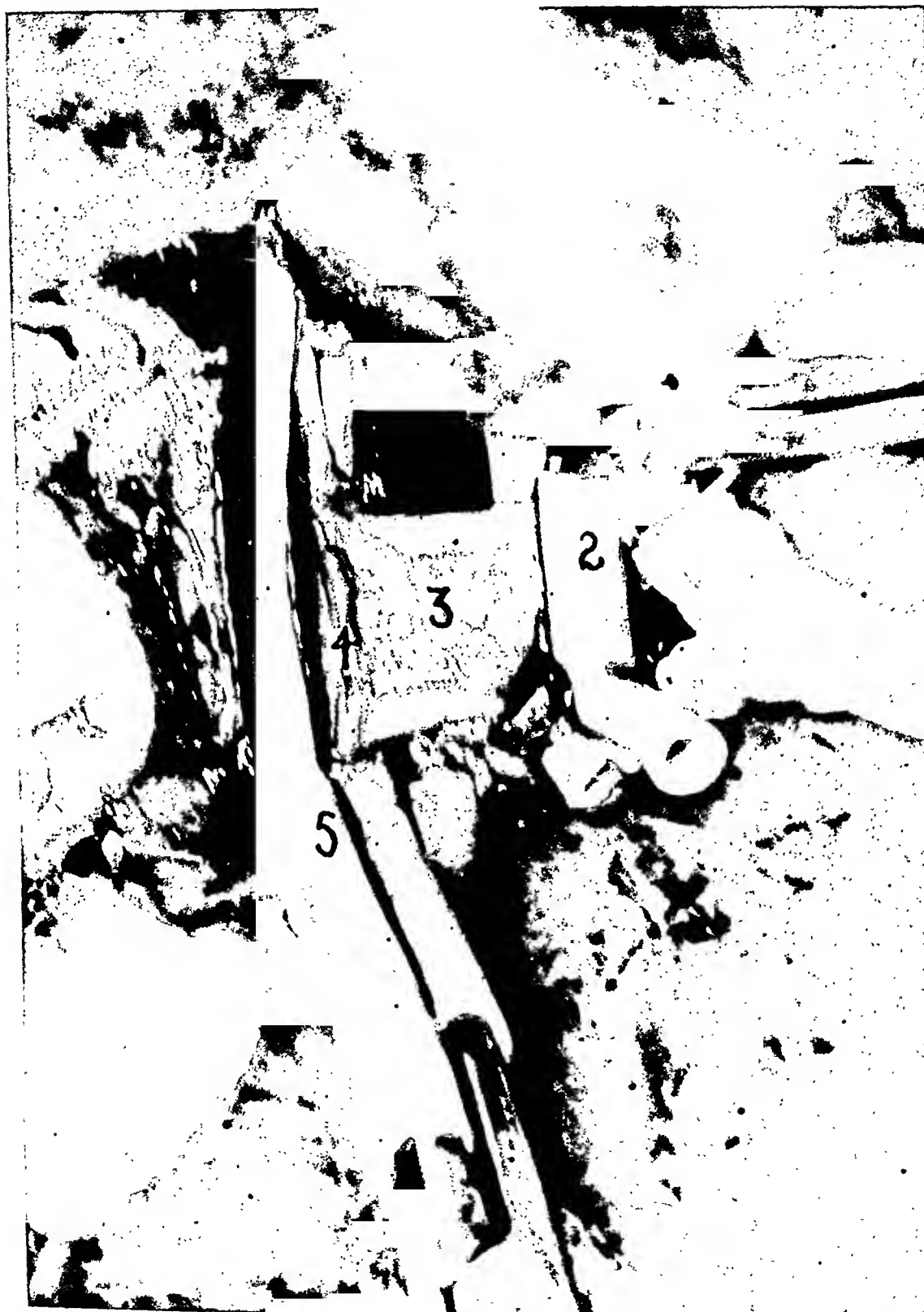


FIG. 4.—Completed anterior layer of anastomosis: 1. Liver; 2. Blalock clamp; 3. Portal vein; 4. Suture line; 5. Kidney clamp on inferior vena cava.



closed with an everting running mattress suture. A single tension suture was placed at each side of the anastomosis and one of the free ends of these sutures was tied to a free end of the anastomatic sutures. During the performance of the anastomosis, the accessible intima of both the inferior vena cava and portal veins were repeatedly irrigated with a heparin-saline mixture (one-half cc. heparin to a medicine glass full of saline), as suggested by Blakemore.<sup>7</sup> With the good exposure afforded by this approach, the curve of the needle on the No. 00000 braided black silk proved to be most satisfactory.



FIG 5—Anastomosis shown after removal of clamps: 1. Liver; 2. Portal vein; 3. Suture line; 4. Inferior vena cava; 5. Clamp points to right renal vein entering inferior vena cava; 6. Right adrenal gland lies in this area

After the completion of the anastomosis the Blalock clamp was released. There was slight leakage through the small apertures in the vessels made by the passage of the needle. In a few moments, however, the suture line became perfectly dry. The kidney clamp was then removed, and blood was seen to course through the portal vein up into the inferior vena cava very rapidly. The shunt was more than adequate, measuring approximately  $2\frac{1}{2}$  cm. in

diameter, and the strength of the one-layer suture line was put to visible test by the fact that with the patient lying on his left side maximum pull was exerted on the anastomosis by the weight of the intestines. A mixture of plasma and thrombin was injected into the region of the anastomosis. The rent in the posterior peritoneum was sutured. Fifty thousand units of penicillin was placed in the peritoneal cavity and another 50,000 units in the chest. The peritoneal cavity was closed. The diaphragm was repaired with interrupted imbricating mattress sutures, and the chest and abdomen were closed in layers. An intercostal drainage tube below the line of incision was placed in the chest and connected with a water-sealed drainage system. Cotton suture technic was employed throughout. Actual operative time was approximately four hours. The author feels quite sure, however, that in the future the portacaval shunt can be performed in well under three hours by means of this approach.

The severe portal hypertension that existed in this patient and the great speed with which the blood rushed through the anastomosis, coupled with the precaution of having excised a portion of the inferior vena cava before commencing the anastomosis gave assurance that the shunt would not close off, and argued against the need for postoperative parenteral administration of heparin.

Three pints of blood were used during the operation. Postoperatively, the patient was placed in the Trendelenburg position so as to prevent gravity drag on the portal vein; this was maintained for 48 hours, at which time it was felt that sufficient adhesion formation had fixed the portacaval anastomosis and the adjacent tissues in a favorable, tensionless position, and obviated the possibility of postoperative angulation due to variations in posture. The patient received parenteral fluids for three days and was permitted out of bed on the fourth postoperative day. A detailed account of the medical aspects of this case and the results obtained by this procedure will be reported in a future communication.

#### DISCUSSION

A direct anatomic approach to the hilar structures of the liver seemed a logical and necessary step if surgeons hope to advance and popularize surgical procedures on these structures. The writer felt, for instance, that portacaval anastomosis, physiologically valuable in the treatment of portal hypertension, was not taking its proper place because of a technically difficult and unbelievably time-consuming approach requiring from 7 to 12 hours by the abdominal route. The average physician hesitates to entrust a bad risk patient to the average surgeon for so traumatic a procedure. With the above described approach, however, portacaval anastomosis becomes a relatively simple operation, carrying no more technical difficulty than already mastered abdominal and thoracic operations.

An objection to the thoraco-abdominal approach may be raised by those who feel that it is imperative to obtain pressure readings of the portal system at the time of operation, and that a surgeon should be free to make a choice

between portacaval and splenorenal anastomosis. In most instances, a diagnosis usually can be made preoperatively or at a previous operation. However, the objections would be well taken were it not for the fact that in the thoraco-abdominal approach the abdominal portion of the incision could be made first, and pressure readings taken. If a splenorenal anastomosis is decided upon, the incision could be enlarged to the left side so as to permit adequate exposure for this procedure. If, on the other hand, a free choice exists, then by all means the larger portacaval shunt is desirable and could be performed more easily than the splenorenal shunt, by extending the incision over the costal cage. By means of the thoracoabdominal approach the portacaval anastomosis is certainly easier to perform than a splenorenal shunt, where often exsanguinating hemorrhage is encountered in dealing with an enlarged spleen complicated by perisplenitis and extensive collateral circulation. Moreover, the thoracoabdominal approach reduces to an absolute minimum the handling of bowel, and thereby avoids troublesome ileus.

Because of the excellent exposure of the entire length of the common duct, the approach described is strongly urged for reparative common duct surgery where reconstruction work must be carried out close to the hilum of the liver. It will also prove most useful for easy and complete exposure of the right adrenal and should result in a wider scope of activity in dealing with conditions involving this gland.

#### SUMMARY

A new approach for a portacaval anastomosis, common duct surgery, and right adrenal gland surgery has been described. The advantages of this transthoracic, thoraco-abdominal exposure are as follows:

1. The structures in the hepato-gastric omentum are approached from the lateral aspect, thereby presenting the portal vein to the side of the common duct and the hepatic artery.

2. The liver can be dislocated into the right hemi-thorax, since the diaphragm no longer restricts mobilization of the liver as it does in the abdominal approach.

3. Access to the hilum of the liver is simplified, enabling ligation of the right and left branches of the portal vein instead of the portal vein itself. High ligation not only affords a longer segment of portal vein for anastomosis but reduces the chances for thrombosis formation in a blind venous pouch.

4. Exposure is wide because of the free spread of the ribs and the free communication of the chest and abdominal cavities.

5. The liver hilum structures and the inferior vena cava are presented more superficially than when the patient is placed on his back.

6. With the patient lying on his left side the suture line supports its maximum tension, and dependability may be visualized at the time of operation.

7. Handling of the intestines is avoided, thereby reducing to a minimum postoperative ileus.

8. The troublesome venous collateral circulation is easily coped with by this direct exposure; more importantly, it is practically avoided.

9. By employing the thoraco-abdominal route, portacaval shunts will be favored over the less desirable splenorenal junctures, and will make for a less hazardous postoperative course since the use of heparin is scarcely called for with the larger portacaval anastomosis.

10. Pressure reading of the portal system can be taken at the time of operation simply by performing the abdominal portion of the thoraco-abdominal wound first.

11. Little chance for postoperative incisional hernia exists, since the abdominal portion of the wound constitutes a small part of the entire incision.

12. Excellent exposure is offered by this route both for reconstructive surgery of the common duct where the injury is close to the hilum of the liver and for right adrenal gland surgery.

### CONCLUSIONS

The thoracoabdominal approach as described by the author and as successfully performed by him on a 45-year-old male patient with cirrhosis of the liver appears to be the procedure of choice in dealing with portacaval anastomosis, reconstruction of the common duct close to the hilum of the liver, and surgery of the right adrenal gland.

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The photographs presented in this article were taken by Dr. Charles P. Bailey and Miss Mildred Updite, R.N.

# THE RIGHT THORACO-ABDOMINAL APPROACH\*

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THE NEED FOR AN APPROACH to the contents of the right upper quadrant of the abdomen which would provide more satisfactory exposure, has long been appreciated. This has been especially true in regard to patients with biliary tract disease who are, as a rule, quite obese.

Numerous surgeons, including one of us (J. P. H.) had occasion during the war to operate upon patients with wounds involving both the thorax and abdomen which required exploration of both cavities, on the right side as well as on the left. Thus far, we have not heard of the elective use of an approach to the right upper quadrant via a segmental thoraco-abdominal incision, although Carter has speculated about the possibilities of such an incision for lesions of the right lobe of the liver.

For an appreciable period, we have had under consideration the right thoraco-abdominal approach which, it was believed, might offer the solution sought to the problem of exposure. At first, it seemed apparent that the right lobe of the liver would certainly become more readily accessible for safe surgical attack, not only because of the exposure of the lobe *per se* but because the inferior vena cava might also be reached and temporarily controlled during the process of excision, *above* the liver as well as below.

Further, it occurred to us that in procedures upon the biliary tract through the conventional abdominal route, it was primarily the immobility of the costal margin which prevented good exposure. By using the segmental thoraco-abdominal incision, the costal margin might thus be eliminated as a barrier. The right lobe of the liver could then be gently rotated backward and upward into the lower thorax through a radial diaphragmatic incision. As a result, the biliary tract and porta hepatis, which usually nestle deep in the posterior part of the right upper quadrant, overhung by the liver, would be exposed easily and consistently in a manner heretofore achieved only occasionally and then, as a rule, in thin patients.

With these ideas in mind, the incision was first used in the anatomy laboratory. Through it, a complete dissection of the extrahepatic biliary tract, caval, and pancreatico-duodenal regions was performed. Although the tissues were fixed and the liver lobe rigid, we were encouraged to believe that this approach might indeed be worthwhile.

The maneuver was next tried in dogs. Because of the lobulated nature of the canine liver, it was necessary to reserve judgment as regards the mobility of the liver in man, but these animals served to illustrate that if the

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liver could be readily retracted as believed, then certainly the anatomic parts to be dealt with would be adequately uncovered.

The last phase of the preliminary work was done in the postmortem room where the tissues, when relatively fresh, are as nearly of the same consistency as in the living patient. This work demonstrated clearly that the procedure deserved clinical trial.

It was decided that the first case should be a simple cholecystectomy in order that if the patient presented any complication not foreseen by the pre-

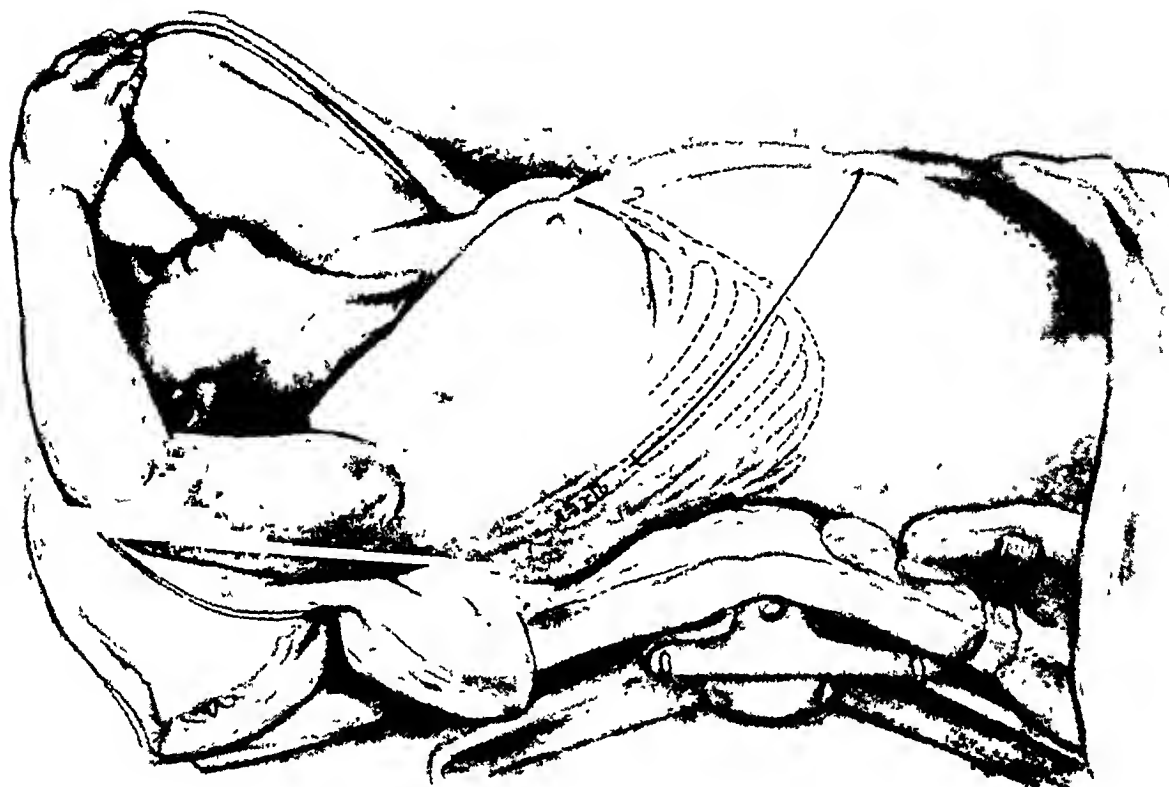


FIG. 1.—The patient is placed on a horizontal table with sand bags beneath the right shoulder and buttock and with the abdomino-thoracic region centered over the "break." The table should be of the type which permits rotation in its long axis. This movement facilitates access to any part of the wound.

liminary work, it might still be feasible to remove the organ through the abdominal segment of the incision in a more nearly conventional manner. However, the most obese patient available was selected in order to put the presumed advantages of the procedure to real test.

#### CASE REPORT

On May 7, 1947, a 45-year-old, Para IV, Puerto Rican housewife presented herself because of severe right upper quadrant pain of 24 hours' duration. For 14 years she had suffered from intolerance to fatty foods with indigestion and belching. This was sometimes accompanied by right upper quadrant and epigastric discomfort which infrequently radiated through to the scapular region. During attacks, she occasionally had nausea and vomiting but had never had chills, fever or jaundice. The episode which brought her to the hospital seemed more severe than previous ones. She vomited more intensely and felt "chilly" but did not record her temperature. The pain radiated to the

lower angle of the right scapula and to the right shoulder. She had noted that her urine was darker than usual, but two stools passed after onset of her present illness were normal in color. She had never had typhoid fever. Past history and inventory of systems were otherwise non-contributory.

*Physical Examination.*—Temperature 100.2; Pulse 80; Weight 195 lbs.; Height 61."

The patient was a well developed, very obese woman in no distress. The skin and sclera were clear. The abdomen was protuberant with a very thick abdominal wall. There was moderate spasm in the right upper quadrant with direct and rebound tenderness in that area. No mass or viscus was palpable. The remainder of the physical examination revealed no further relevant abnormal findings.

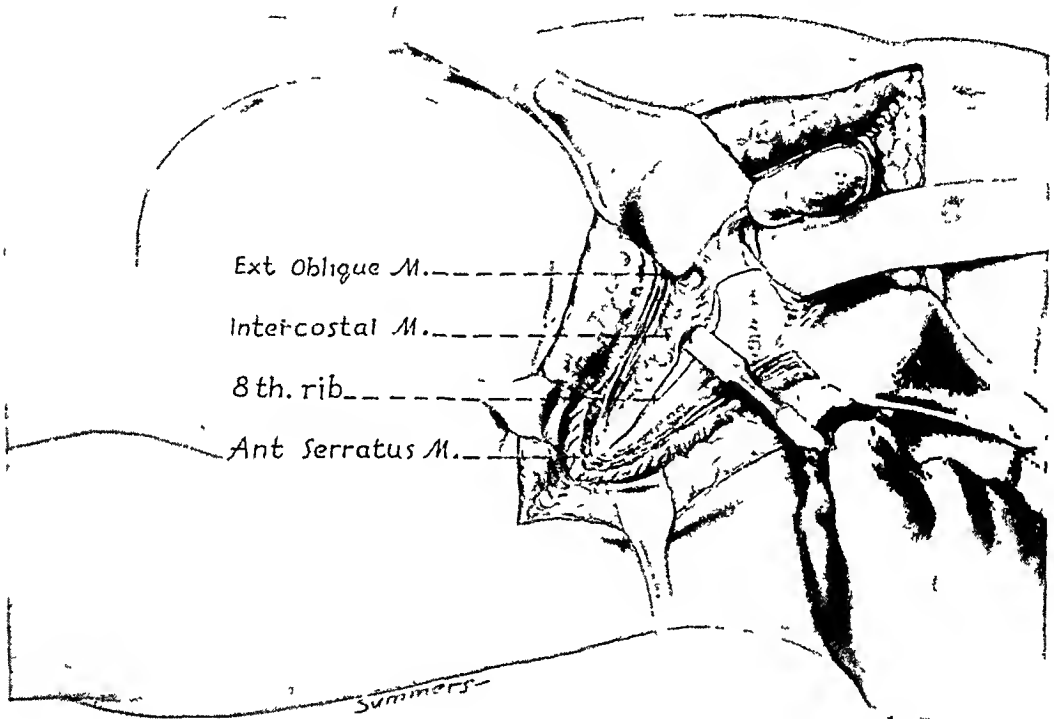


FIG. 2—The abdomen has been entered; an exploration can be made through this segment of the wound. The 8th rib is then resected subperiosteally after which the costal margin is divided. Some operators might prefer an intercostal approach.

The impression at the time of admission was:

1. Acute cholecystitis superimposed on chronic cholecystitis with cholelithiasis
2. Obesity.

*Laboratory Findings.*—Studies following her admission revealed a serum bilirubin of 3.6; alkaline phosphatase 6.4; white blood count 10,100 with 53 per cent polymorphonuclears; the urinalysis showed four plus bile. An electrocardiogram was negative as was a chest film. On symptomatic care and a low fat, low caloric diet, the patient improved. A cholecystogram on the 11th hospital day revealed the presence of dye in the gallbladder with a 3 cm area of translucency, which was interpreted as a single large stone. She was, therefore, prepared for cholecystectomy and operated on the 14th hospital day.

*Pathologic Findings.*—The gallbladder was moderately distended and contained several large faceted stones, one of which was tightly impacted in the ampulla. The cystic duct was thickened but the common duct showed no evidence of disease. The duodenum, head of the pancreas, right lobe of the liver, and stomach presented no abnormalities.

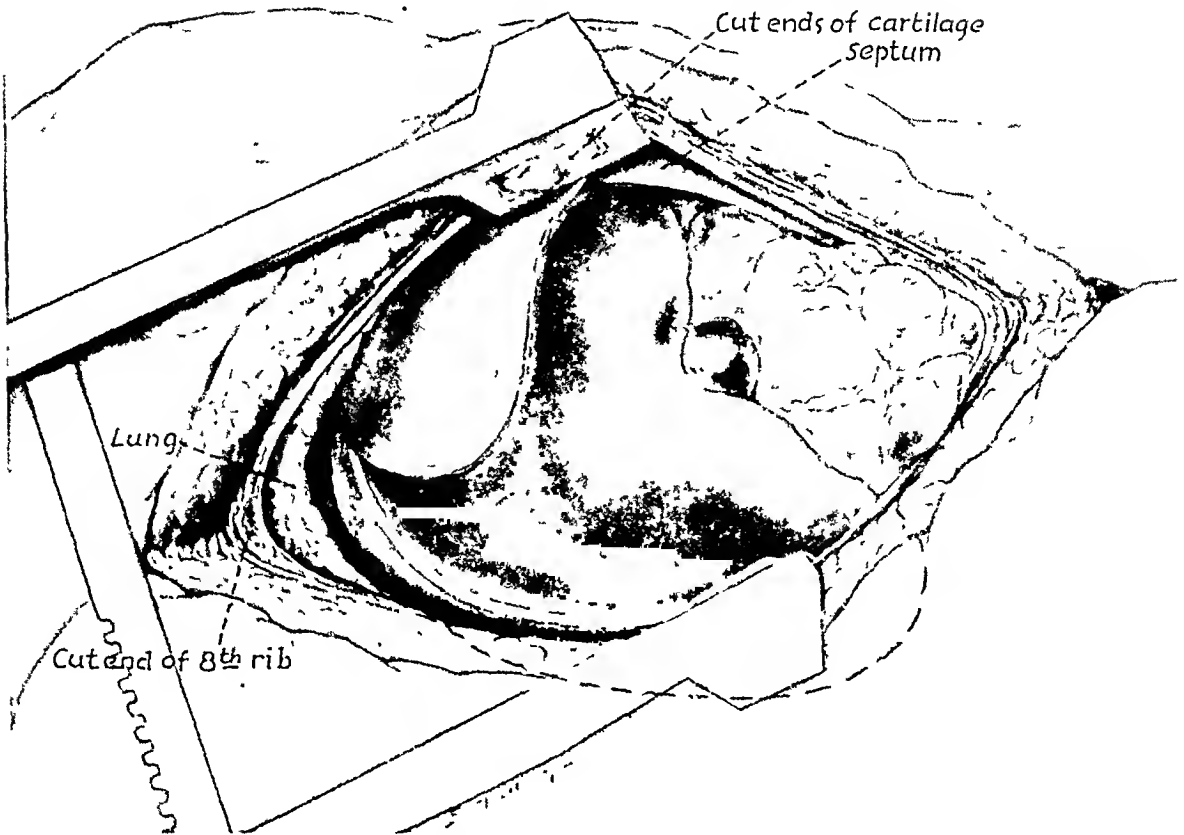


FIG. 3.—The addition of the radial incision to the diaphragm, from costal margin to dome, reveals the antero-superior surface of the liver. The lower lobe of the lung is evident above; the gallbladder, fundus and colon appear below. Note the cut edges of the diaphragm which have been separated, along with the mural components of the incision, by the Finochetto retractor.

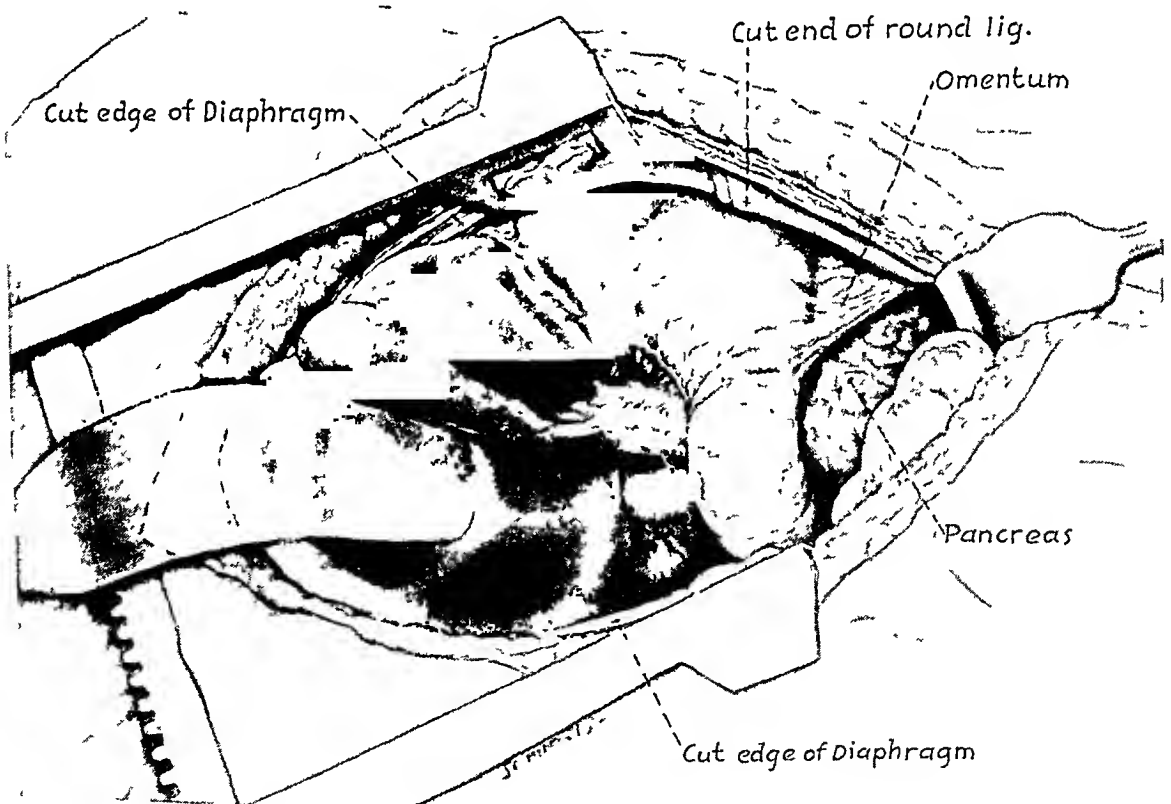


FIG. 4.—The right lobe of the liver has been turned upward through the diaphragmatic defect into the lower chest. The structures formerly overhung by the liver, are thereby uncovered.



*Operative Procedure.* On May 22, 1947, the patient was anesthetized with a combination of agents administered intratracheally. A long curved incision was made overlying the ninth interspace. It extended from the mid-axillary line downward and forward across the costal margin, and over the abdomen to the linea alba at a point 5 cm. above the umbilicus. This incision was carried through the subcutaneous tissue to expose the external oblique muscle and anterior rectus sheath. The latter was divided transversely as was the right rectus muscle. The external oblique muscle was split in the direction of its fibers, whereas the internal oblique, and transversus abdominis muscles were

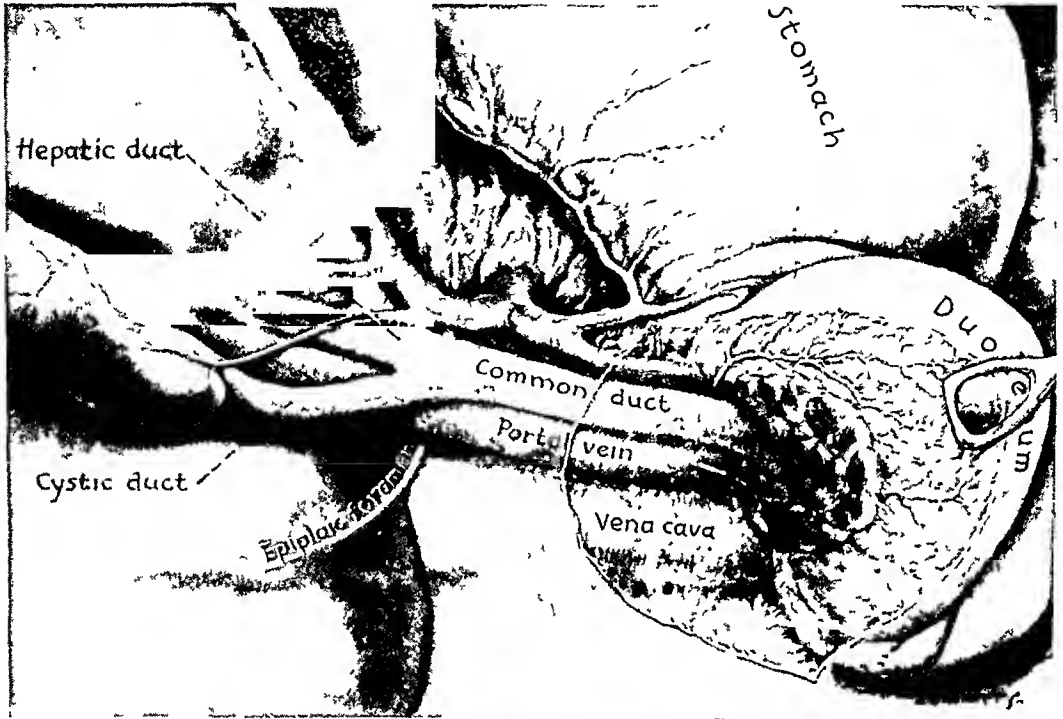


FIG. 5.—This enlargement, which shows the duodenum reflected, was made from a dissection in the postmortem room. It illustrates the extensive exposure of the biliary tree and allied structures, which is possible through this approach.

transected in the line of the incision. The common costal cartilage was divided between the 9th and 10th ribs and the chest entered through the 9th interspace. The abdomen was then entered by means of a radial incision in the diaphragm which extended from its periphery at the point of division of the costal margin, to the right dome. Following this the peritoneum was divided throughout the length of the abdominal segment of the wound. A Finochietto retractor was placed between the 9th and 10th ribs and spread. In this manner, the wound was held wide open without other retraction. Next, the right lobe of the liver was gently rotated upward through the diaphragmatic defect into the right lower chest, exposing the gallbladder, the porta hepatis, the gastrohepatic omentum, the vena cava and the pancreatico-duodenal region admirably, in spite of the patient's great obesity. The stomach and hepatic flexure were packed off with moist abdominal pads; several filmy adhesions between the duodenum and gallbladder were divided. The common and cystic ducts were identified and isolated as were the common hepatic duct, and the right and left hepatic ducts with their accompanying vessels. This dissection permitted unusually extensive study of the duct system. The cystic duct was then divided between clamps. The proximal end was ligated with a transfixion suture of No. 000 Deknatel. The cystic artery was also divided and ligated with the same material. The

gallbladder was dissected from the liver, from ampulla to fundus, without difficulty after which the bed was repaired with interrupted silk sutures. The peritoneum over the cystic duct stump and in the region of the porta hepatis was also approximated by means of interrupted sutures. After the liver had been replaced in its normal position, a cigarette drain was inserted into Morrison's pouch and brought out along the gallbladder bed through the abdominal part of the incision. The diaphragm was then closed with interrupted No. 000 Deknatel. A single suture of No. 0 Deknatel was used to approximate the cut edges of the costal margin. The thoracic and abdominal mural components of the incision were then closed anatomically with interrupted sutures of No. 000 silk. The patient's condition during and after operation was excellent.

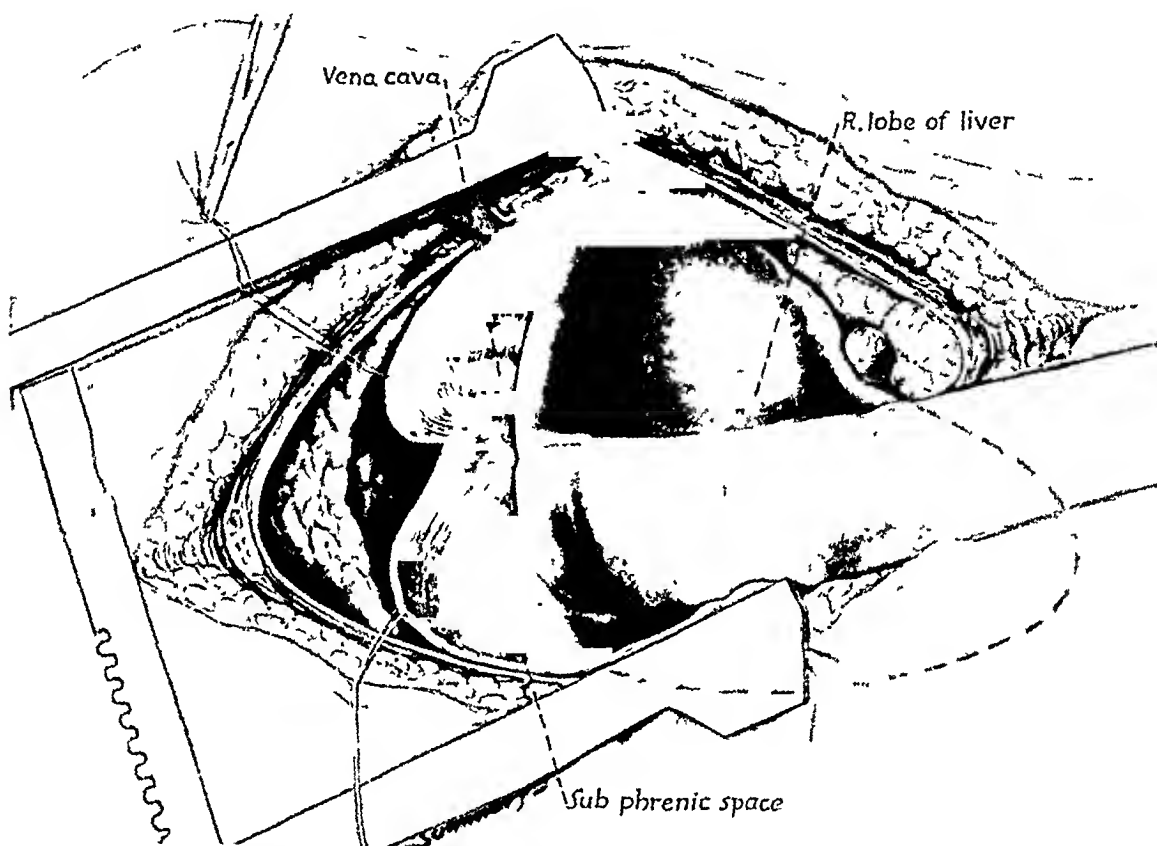


FIG 6.—The liver has been retracted downward; the diaphragm edges are suspended by means of silk sutures to show the position of the inferior vena cava *above* the liver. The liver lobe is also outlined to demonstrate its position. (See Text.)

Postoperatively, the temperature rose to 100.2 on the first day; 102.6 on the second; 101.8 on the third and then declined gradually to normal. This fever was due in part to transient atelectasis of the right lower lobe, which responded to coughing efforts. Her convalescence and wound healing were otherwise favorable and uneventful. She was discharged on the 15th postoperative day. She has been followed in the outpatient clinic since operation and has remained well.

#### DISCUSSION

This cholecystectomy was performed with ease in spite of the patient's unusual obesity. There was no tugging upon retractors and no difficulty in exposure. The right lobe of the liver was easily rotated upward into the lower thorax and produced no change in the patient's general well being. There was no torsion of the inferior vena cava or structures of the hepatic

trinity. The cystic duct and artery were dealt with under direct vision in a wide open wound, rather than in one overhung by the liver, costal margin and abdominal wall. Not only was the common hepatic duct readily accessible throughout its entire extent, but each of the right and left hepatic ducts was accessible over a distance of  $1\frac{1}{2}$  to 2 cms., permitting unusual certainty in palpating for stones or, had it been necessary, the performance of high biliary-intestinal anastomosis.

The phase of the operation which was potentially the most hazardous, namely, the division of the cystic artery and duct, was rendered less so because of the exposure afforded by the maneuver of displacing the liver into the chest. This latter act is accomplished by turning the right lobe upward and outward so that the inferior surface, which originally faced downward and posteriorly, comes to face anteriorly and still slightly downward. The liver does not rotate as if upon a hinge but readily molds into the position sought in a "fluid" type of movement. During the process, the portal fissure opens in the same manner as a single pleat of an accordion, thus bringing into view a greater extent of the biliary tree.

Our particular patient brought out only one unforeseen difficulty. The cut edges of the diaphragm retracted so that at the peripheral part of the diaphragmatic incision, it was not easy to suture the edge because of the friable liver beneath and the unyielding rib superficially. It is probable that a rib resection would make closure less difficult.

We do not believe that this approach should supplant the ordinary paracostal or right rectus incision for cholecystectomy in the average instance but it does offer an additional degree of exposure for exceedingly obese cases. It should be useful in secondary and tertiary operations upon the biliary tree, when anatomical landmarks have been obliterated by adhesions from previous procedures. It would seem ideal for plastic operations upon the duct system. Secondly, the pancreatico-duodenal region was also superbly exposed, though this latter region was not the one in which we were primarily interested. We have witnessed numbers of pancreatico-duodenectomies through both transverse and vertical abdominal incisions in which that operative field was less well exposed than in this case. Thirdly, the portal vein and inferior vena cava are readily evident throughout much of their proximal extent; as a result the incision should be useful in performing portocaval anastomosis.\* Fourthly, the right lobe of the liver is exceptionally well exposed and its removal might be made safer by the temporary control of the inferior vena cava *above* the liver, as well as below. Fifthly, in selected patients who have an unusually high diaphragm, in addition to their other indications for the approach, it is possible that the contents of the right upper quadrant might be satisfactorily exposed through the chest and diaphragm alone, without the addition of the abdominal mural segment of the incision. Thus the gallbladder might be more

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\* This approach has recently been used by Dr. Arthur Blakemore in a case of portal hypertension. Portocaval anastomosis was accomplished with excellent exposure. Post-operative recovery was uncomplicated.

easily removed in some cases through the chest than through the abdomen, just as splenectomy and gastrectomy are sometimes more satisfactorily accomplished from *above*, on the left side of the abdomen. The incision should also be valuable in the occasional inflammatory or neoplastic lesion which traverses the diaphragm to involve both the right lower lobe of the lung and the right lobe of the liver.

Lastly, if one encounters unusual difficulty while operating upon right upper quadrant structures through a conventional abdominal incision, the segmental mural and diaphragmatic components may be added to obtain the additional exposure which is so valuable in time of need. This combination of ordinary abdominal incision, plus subsequent addition of the segmental components, has been used to advantage on the left in numbers of cases, without compromise of circulation of the flaps so formed.

#### CONCLUSION

We believe that the right thoraco-abdominal segmental approach offers valuable additional exposure in properly selected operations upon the biliary tree, the pancreatico-duodenal region, the portocaval region and the right lobe of the liver.

If unexpected technical difficulties are encountered in the right upper quadrant and additional exposure would be advantageous, it can be used as an adjunct to the ordinary right rectus, paracostal, or transverse abdominal incisions.

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# EXPERIENCE WITH THREE THOUSAND CASES OF BRACHIAL PLEXUS BLOCK; ITS DANGERS

## Report of a Fatal Case

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IN JULY OF 1936 we published a paper dealing with 250 cases of Block Anesthesia of the Brachial Plexus.<sup>20</sup> We expressed at that time our surprise at the lack of interest which the majority of surgeons manifest in this procedure. Moreover, we pointed out that a definite dearth of literature existed concerning brachial plexus block. Shortly after our report in July of 1936 a thesis for doctorate<sup>15</sup> was published dealing with 403 cases of block anesthesia of the brachial plexus.

Owing to the great number of war casualties with wounds of the upper extremities which came under our care at the Orthopedic Services of the Casa de Salud-Valdecilla and the Hospital Militar Cantabro, we have been able to compile 3000 cases in which block anesthesia of the brachial plexus has been used. In the present paper we shall not discuss fundamental considerations of this procedure, nor anatomic details and technics. Instead, drawing from our experience, we shall confine ourselves to a discussion of the accidents encountered in the use of brachial plexus block, one of which in our series proved fatal. We hope, also, to elucidate the causes of such accidents; thus aiding in their prevention and raising the procedure of brachial plexus block to a more deserved place in the surgery of the upper extremity.

In practically all of our cases, the technic described by Kulenkampff,<sup>14</sup> and expanded by us in our previous paper, was employed.

The supraclavicular region contains important anatomic structures with which we must be completely familiar if we would obviate accidents. It is situated over the dome of the pleura and is traversed by major nerves and blood vessels. This region is also noted for the rapidity with which drugs are absorbed by it; hence the dosage and toxicity of the anesthetic agent should be carefully borne in mind. With the foregoing facts as a basis, the accidents encountered in brachial plexus block are classifiable into pleuropulmonary, neural and vascular. However, before discussing these accidents, we shall point out the importance of choosing the proper anesthetic and its dosage. At present we are using novocain "Bayer," a 2 per cent solution "without adrenalin," and in none of our cases have we observed lipotemias or syncopes; only once did a mild degree of cerebral excitation, as is seen in the first stage of ether anesthesia, occur, when the dose exceeded the currently used dose of 20 cc., or when the latter dose was employed in children. Reducing the dose to a suitable amount, we have succeeded in obtaining adequate anesthesia in babies as young as one and one-half years of age. On the other hand, when

constrained by circumstances to employ substitutes for novocain, such as, sincaïn, sedocain, alocain, etc., it was not uncommon to observe untoward effects of tachycardia, chills, bouts of sweating, and angina pectoris. In one case, when by error novocain with adrenalin was used, tachycardia and



FIG. 1.—Right supraclavicular region, head being turned to the opposite side; the sterno cleido mastoid and trapezius muscles are drawn aside by means of retractors; the omohyoid and the clavicle are sectioned and the latter is pulled down. (1) brachial plexus, (2) subclavian artery, (3) subclavian vein, (4) 1st rib, (5) clavicle, (6) vasculo-nervous plexus of the neck, (7) thyroid, (8) inferior hyoid artery, (9) chain of sympathetic ganglia, (10) trapezius, (11) sternocleidomastoid muscle, (12) posterior scalenus, (13) anterior scalenus, (14) recurrent nerve.

arrhythmia resulted of such a degree, that, though the patient did not expire, death seemed imminent.

To obtain a prolonged anesthesia, we have never employed percain; in all our cases an anesthesia of two hours, produced with novocain, being sufficient. Concentrations of novocain of less than 2 per cent produce poor results, and we deem greater than 2 per cent to be dangerous.

To obviate the untoward effects resulting from both the toxic action of

the drug and from its rapid absorption in the cervical region, we believe it a prudent measure to inject the drug very slowly and to record the rate of the radial pulse.

In the foregoing accidents Coramine has been found efficacious.

*Pleuropulmonary Accidents.* From a careful review of the literature on brachial plexus block, we have gleaned three reports of death following this procedure; namely, Capelle in 1916,<sup>4</sup> Vischer in 1918,<sup>22</sup> and Hering in 1920.<sup>7</sup>

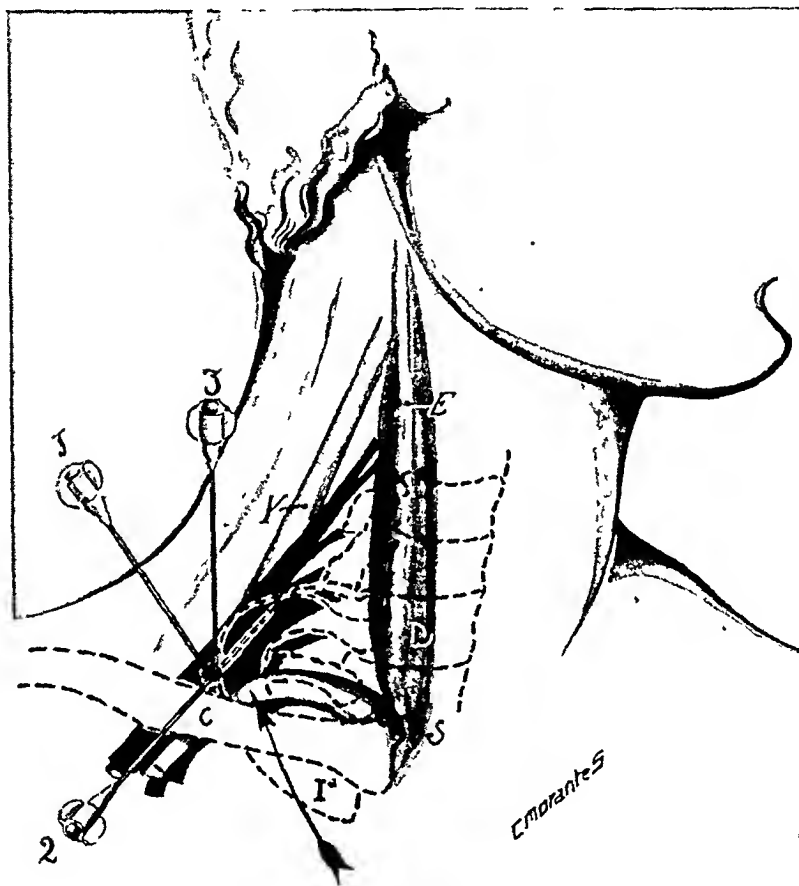


FIG. 2—Technic of Kulenkampff. (1) 1st stage, (2) 2nd stage, (3) 3rd stage. The arrow indicates the point where one should place the index finger to protect the subclavian artery. (S) subclavian artery; (C) clavicle; (E) anterior border of the trapezius; (Y) posterior border of the sternocleidomastoid muscle; I (a) 1st rib.

All of these deaths resulted from trauma to the apical pleural and lung parenchyma. The trauma was produced by incorrect insertion of the injecting needle beneath the first rib as a result of respiratory movement. The supra-clavicular technic of Kulenkampff was used by all these surgeons. Following such trauma there supervened rapidly a subcutaneous emphysema, pneumothorax, hemothorax and dyspnea, successively; and in Capelle's case the patient died on the second day. An autopsy revealed, in addition to pneumo-

sema. All the cases showed emphysema and cardiovascular insufficiency. Weil<sup>23</sup> reported a case of spontaneous recovery following mediastinal emphysema.

On five occasions we punctured the parietal pleura the sibilant sound produced by the intrushing air, however, placed us on guard, and the needle was withdrawn carefully. Roentgenograms disclosed the presence of moderate

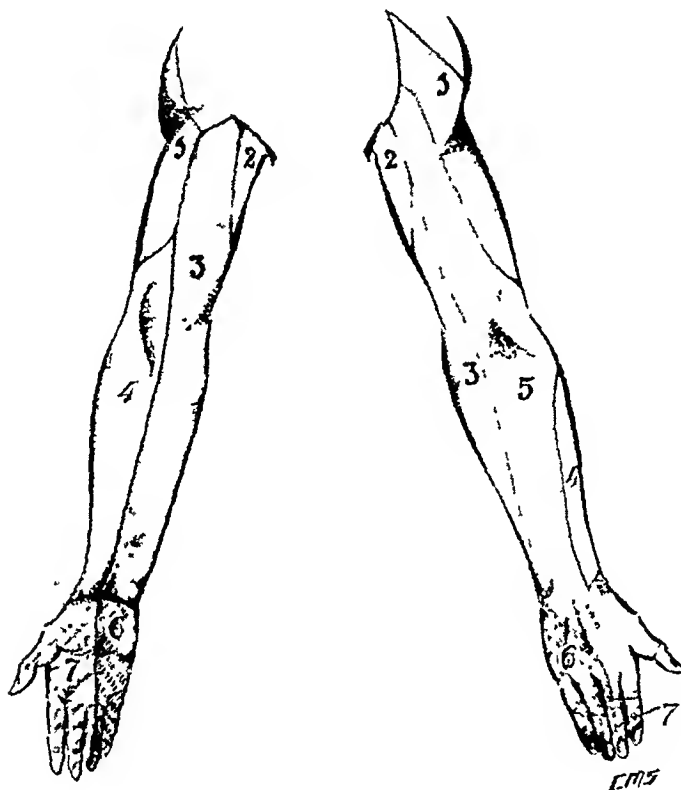


FIG. 3.—Zone of innervation of each of the branches of the brachial plexus. (1) circumflex, (2) accessory of the internal cutaneous brachial nerve and intercostal nerves, (3) internal brachial cutaneous nerve, (4) musculo-cutaneous, (5) radial, (6) cubital, (7) median.

pneumothorax which, together with the consequent dyspnea, subsided in 48 hours.

In order to obviate pleuropulmonary accidents Capelle adopted the axillary route of Hirschel,<sup>8</sup> but as we shall presently point out, this route is no less dangerous than the supraclavicular route. Mulley,<sup>16</sup> in 1919, with the same intention modified the technic of Kulenkampff, placing the point of injection 3 cm. above the clavicle and 2 cm. lateral to the external jugular vein, and maintaining the needle in a more horizontal position. We believe that this modification renders the procedure of brachial plexus block less certain. The same can be said for the infraclavicular technic of Balog,<sup>2</sup> or and of the Anglada Santoni, technic as well as of the Kinn modification.<sup>12</sup>



We consider the paravertebral technic of Kappis<sup>11</sup> to be unusual. To avert pleuropulmonary accidents we maintain that adherence to the technic of Kulenkampff alone is necessary.

*Neural Accidents.* We shall not consider here the transient aphonias and Claude Bernard-Horner syndromes that supervene from the anesthesia of the recurrent laryngeal nerve and of the cervical sympathetic chain respectively. Hemidiaphragmatic paralysis can occur as a result of phrenic nerve block if excessive infiltration of the region, or incorrect technic is practised. We have, however, on four occasions, produced bilateral brachial plexus block without any untoward effects. Siebres<sup>21</sup> and Klauser<sup>13</sup> report similar successes.

Following our first experience with the technic of Kulenkampff, on one patient there resulted a mild contraction and paresthesia of the lower extremity together with a moderate lipotemia. We conjectured that the needle may have entered the spinal canal through an intervertebral foramen.

Of the neural complications that follow brachial plexus block especially interesting are the meralgias with paresthesias which have been pointed out by many authors; namely, Babizki,<sup>1</sup> Raechke,<sup>10</sup> Flesch-Telesius,<sup>3</sup> Hartler and Keppler,<sup>6</sup> Hirschel,<sup>10</sup> Borchers,<sup>3</sup> Pacher,<sup>17</sup> and Hylkema.<sup>10</sup> These complications all subside, some very slowly. In five of our own cases the complications abated in 20 days. In almost all of these cases a tourniquet was employed to obtain ischemia of the operative field; and, as in the case of Babitzki, meralgias did not occur at the site of application of the tourniquet. In some of the cases, displaced bony fragments may have aided in the production of these complications. Lastly, in the cases of Pacher it seems that the trauma produced by the intraneural injection of the anesthetic will explain these complications.

A thesis<sup>15</sup> previously cited, incorporates the results of a study of the effects of brachial plexus block on the chronaxie. We have never been able to observe any alteration.

*Vascular Accidents.* Puncture of the common carotid, subclavian, vertebral, and inferior thyroid arteries can, and, in fact, does occur. It has very frequently happened in our own experience. Simple withdrawal of the needle alone is necessary, when it does occur. At times a hematoma will form, but will disappear with the application of a compression bandage. In one of our cases edema of the upper extremity supervened, but subsided after 48 hours with the extremity in the position of abduction.

Intra-arterial injection of the anesthetic produces only a transient state of anesthesia. On the other hand, intravenous injection is dangerous, for the anesthetic is carried to the heart. Moreover, part of the drug may reach the medulla oblongata and produce cardiorespiratory difficulties. Intravenous injection is eight to ten times more toxic than intra-arterial injection, according to Pauchet,<sup>18</sup> even though only one-sixth of the drug ever reaches the cerebrum. We know of no case of death reported as resulting from this mechanism. In the absence of other explanations we believe that perhaps the single case of death in our own series resulted from intravenous injection of the anesthetic.

**Report of a Fatal Case.** An emaciated woman, age 67, was to be treated for an old fracture of the clavicle at the junction of its middle and inner thirds. The fragments were misplaced and an exuberant callus, the size of an orange, had formed. The patient presented no signs nor symptoms suggestive of pleuropulmonary disease. The supra-clavicular technic of Kulenkampff was to be employed. But due to the abnormal anatomic conditions that prevailed, the pulse of the subclavian artery, which is a landmark, could not be felt and a point above the customary midpoint on the clavicle was elected. The needle was directed obliquely to avoid the obstacle presented by the callus, and perhaps in searching for the brachial plexus, the subclavian vein was entered. We suspected that intravenous injection had occurred, when the patient became pallid and cold, and her pulse became weak. The patient lost consciousness, and died in two minutes, despite the

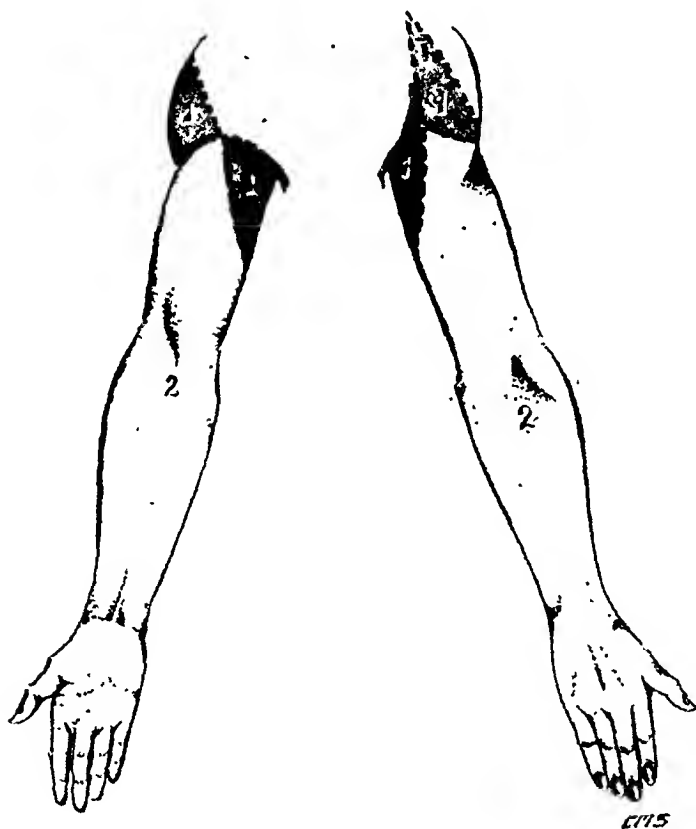


FIG. 4.—Zones of anesthesia of the brachial plexus. (1) Hypoesthesia corresponding to the territories innervated by the branches of the circumflex nerves, 1st and 2nd intercostals. (2) complete anesthesia.

use of cardiovascular tonics and artificial respiration. The anesthetic used was 25 cc. of 2 per cent novocain.

An autopsy performed by Doctor Sanchez-Lucas of the Casa de Salud-Valdecilla, failed to disclose any lesion that would explain this fatality. We believe that the drug entered the venous system through the subclavian vein, was carried to the heart, and subsequently produced its mischief in the central nervous system.

This accident, though fatal, is insufficient to make us abandon this procedure which is so beneficial to the patient and so helpful to the surgeon. In another article we have discussed the advantages of brachial plexus block, and hence we shall not do so here.

Since this fatality, we have successfully employed brachial plexus block in more than 1200 cases. The supraclavicular technic of Kulenkampf was used, and we are favoring this technic more and more each day. We consider the infraclavicular technic of Balog or that of Anglada, Santoni, and above all, the axillary technic of Hirschel to be very dangerous. Our reasons for this statement are that the artery and vein are in proximity in the infraclavicular

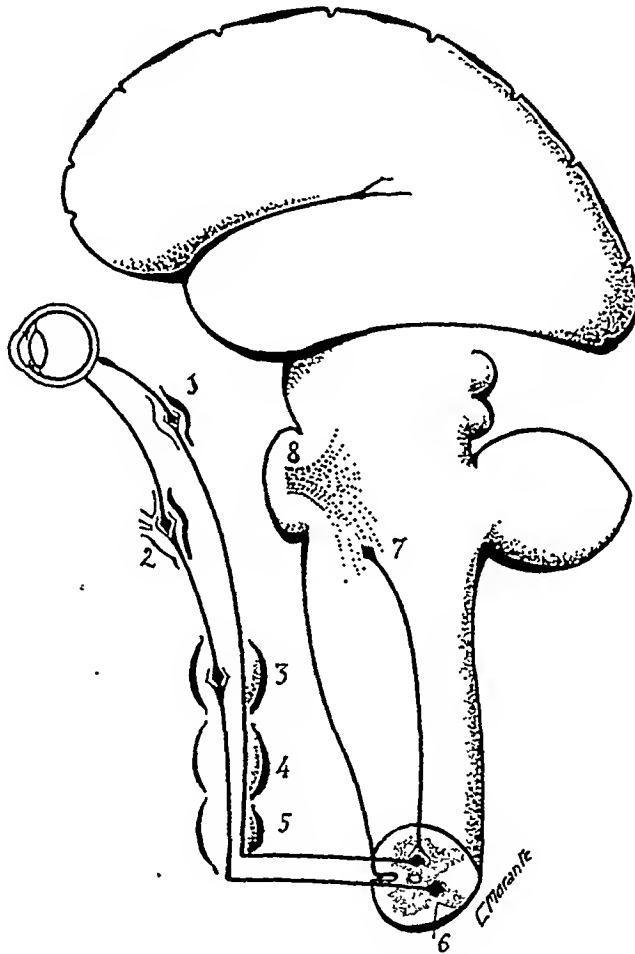


FIG. 5.—Claude Bernard-Horner syndrome. (1) ciliary ganglion, (2) Gasserian ganglion, (3) superior cervical ganglion, (4) median cervical ganglion, (5) inferior cervical ganglion, (6) cilio-spinal center of Budge, (7) Oculo sympathetic bulbar center, (8) descending root of the trigeminus.

region, and that the nerves of the plexus form a network around the vein at the level of the axilla; thus the veins are more easily exposed to accidental puncture.

All of the cases of death and accident, including our own, can be imputed to errors in technic which are easily averted. To present the dangers attending brachial plexus block, and a few methods of preventing them, has been the object of this paper.

SUMMARY

This article, based on a series of 3000 cases, treats of the dangers attending brachial plexus block. It completes a study of this method which was begun with a former publication. We prefer the use of 20 cc. of novocain (2 per cent) without adrenalin. The supraclivacular technic of Kulenkampff is followed, and the dangers attending the infraclavicular technics of Balog, Anglada, Santoni, and the axillary technic of Hirschel, are pointed out. A consideration of meralgias with paresthesias as observed by different authors has been given. To three cases of death following brachial plexus block gleaned from the literature, we add our own case which is of a different origin. We indicate methods of relieving accidents and of obviating them. We believe this type of anesthesia is preferable for all surgery of the upper extremity.

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# FEMORAL HERNIA: A TECHNIC OF REPAIR\*

J. E. STRODE, M.D.

THE CLINIC

HONOLULU, T. H.

IT HAS BEEN ASSERTED that there have been more than one hundred methods described for repairing femoral hernias. This fact seems to indicate that no one method has proven to be universally satisfactory. The method of repair to be described in all probability has been used before but, if so, I have been unable to find reference to it in the literature. If this method has been published it has not been given the publicity it deserves and this is my reason for adding to the already voluminous literature covering the subject.

There are two schools of thought regarding the extent of the operation necessary for cure of femoral hernia. First, those who believe that high ligation and extirpation of the sac is all that is necessary and, second, those who believe that, in addition to this, an attempt should be made either to obliterate the femoral canal or to close off its proximal opening through which the hernia has protruded. It is my belief that the second premise is the one more nearly correct.

It is very difficult if not impossible to determine just how frequently recurrences do occur following any type of repair, first, because femoral hernia is not a common condition and any one surgeon does not have the opportunity of following a large series of cases in which he has used a given technic of repair and, second, because it is difficult to get an accurate follow-up of the cases operated upon over a long period of time.

Shelley's<sup>1</sup> report on the patients with hernia observed at St. Luke's Hospital, New York, from 1916 to 1935, inclusive, is the largest series I have been able to find. This included 238 femoral hernias which comprised 2.35 per cent of all hernias seen. One hundred and forty of these, after primary repair, were examined postoperatively for nine months or longer. The recurrence rate was 3.6 per cent. Thirteen cases with secondary repair showed a recurrence rate of 15.4 per cent.

Dickson<sup>2</sup> comments as follows: "Most writers believe that femoral hernia is a simple surgical problem with satisfactory results. A smaller group believes that the recurrence rate is high and the true results of operation hard to estimate because of inadequate follow-up. Recurrences have been stated by various authors at rates of from 4 to 30 per cent. Extremely low figures are probably incorrect because of the difficulty of following cases after operation."

Ochsner,<sup>3</sup> in 1906, wrote, "It is a well-known fact that it is practically impossible to keep a circular opening in any part of the body from closing

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spontaneously unless it be lined with a mucous or a serous membrane." Therefore, in the usual femoral hernia repair he advised only cleaning out the femoral canal and high ligation and excision of the sac. When one considers how rigid the anatomic structures surrounding a femoral hernia are, it is difficult to understand how such an opening can close spontaneously.

Russell<sup>4</sup> in 1926, discussing femoral hernia, reached these conclusions: "Closure and abolition of the sac by separation and firm torsioning from below is in my opinion by far the safest and simplest and best method of dealing with it."

More recently, in 1942, Waugh and Hausfeld<sup>5</sup> recommended simple excision of the sac without closing the femoral ring or canal.

Many other references could be cited favoring the simple type of repair.

On the other hand, the majority of surgeons advocate, in addition to high removal of the sac, some procedure directed at obliteration of the femoral canal or closure of its proximal opening. Such pioneer observers as Bassini, Ferguson, Halsted, Moschkowitz, Andrews and a host of others since their time have contributed various methods of bringing this about.

Suturing Poupart's ligament to the pectineus fascia or to Cooper's ligament (Shelley<sup>1</sup>) has been a favorite method. Filling the femoral canal with fat derived either from resected omentum or from the abdominal wall, using the resected sac, or filling the canal with catgut are methods that have been described. Bone pegs, staples, screws, transplanted fascia, and osteoplastic flaps from the pûbes have had their advocates. The femoral opening has been closed by utilization of the transversalis fascia (Dickson<sup>2</sup> and Harkins and Swenson<sup>6</sup>) by turning in a flap of the external oblique aponeurosis (Andrews<sup>7</sup>), by suturing the conjoined tendon to the pectineus fascia or Cooper's ligament (Lotheissen<sup>8</sup>) and by other methods too numerous to recount at this time.

Attempts at closing the femoral canal by suturing Poupart's ligament or the conjoined tendon to the pectineus fascia or Cooper's ligament have the common weakness of suturing tissues under tension and in all probability in the majority of instances those structures in time return to their original positions, leaving the femoral canal as patent as before its attempted closure.

Transversalis fascia is a valuable adjunct to the repair of both inguinal and femoral hernias, when this structure is sufficiently developed but unfortunately it commonly is least evident when most needed. The same may be said of the aponeurosis of the external oblique and the pectineus fascia so it is well to have in mind several methods of procedure that may be applicable to the individual case.

There are two methods of approach commonly used in the repair of femoral hernias; one below Poupart's ligament and the other above, using an incision similar to that used in the repair of an inguinal hernia. The latter method of exposure, in almost everyone's experience, is far preferable to the former, though a combination of the two may be desirable, particularly when dealing with strangulated intestine.

Before taking up the details of the method of repair of femoral hernia to

# FEMORAL HERNIA

FIG. 1

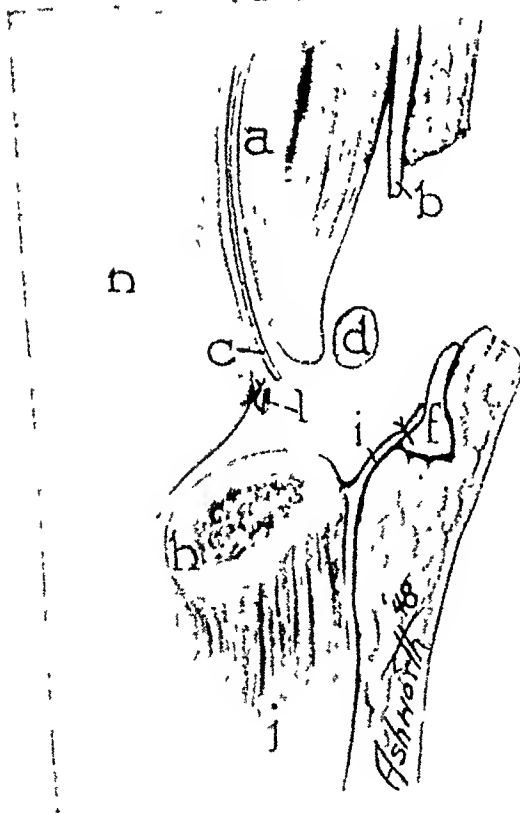
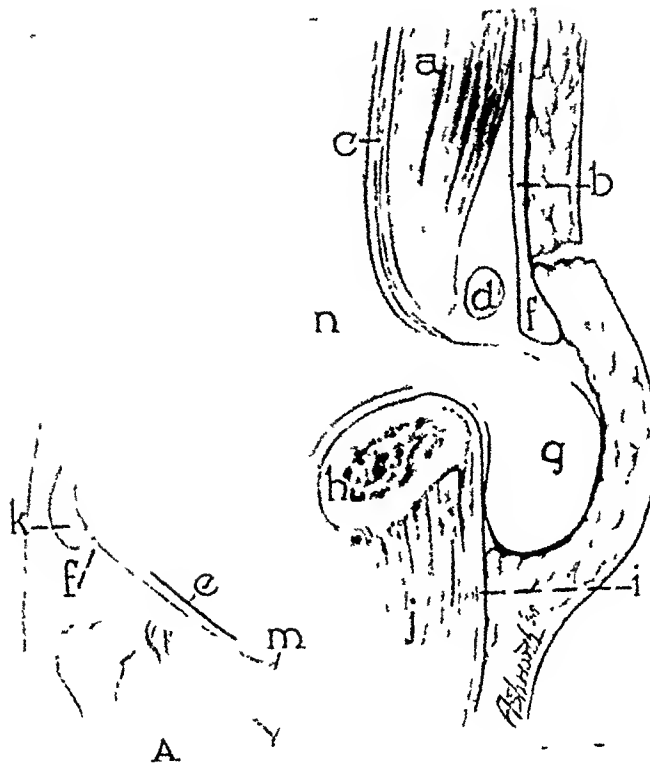


FIG. 2

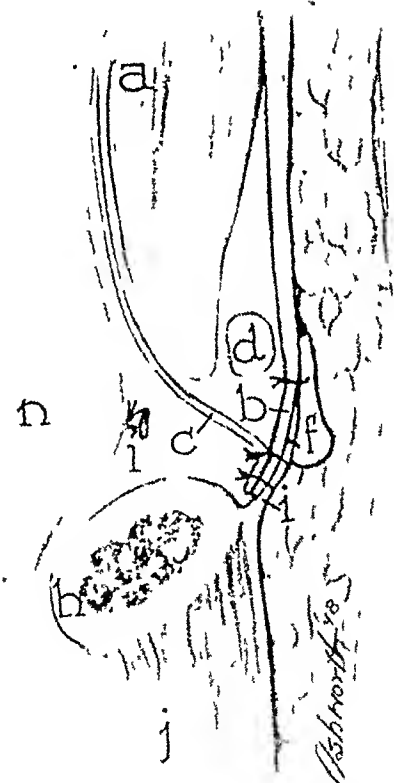


FIG. 3

FIGS. 1, 2, 3.—Drawings showing the incision, sagittal section of a femoral hernia with its anatomic relations and the technic of using these structures in its repair.

- a. Internal oblique muscle
- b. Aponeurosis of external oblique muscle
- c. Transversalis fascia
- d. Round ligament
- e. Incision
- f. Poupart's ligament
- g. Hernia sac

- h. Pubic bone
- i. Pectineus fascia
- j. Pectineus muscle
- k. Anterior-superior spine of ilium
- l. Neck of sac ligated
- m. Spine of pubis
- n. Peritoneum



be described, it will be advantageous to review briefly the anatomy of the parts concerned.

The femoral ring and femoral canal as such do not normally exist since the femoral vein lies in contiguity with Gimbernat's (lacunar) ligament. However, when a femoral hernia develops by the protrusion of abdominal content,

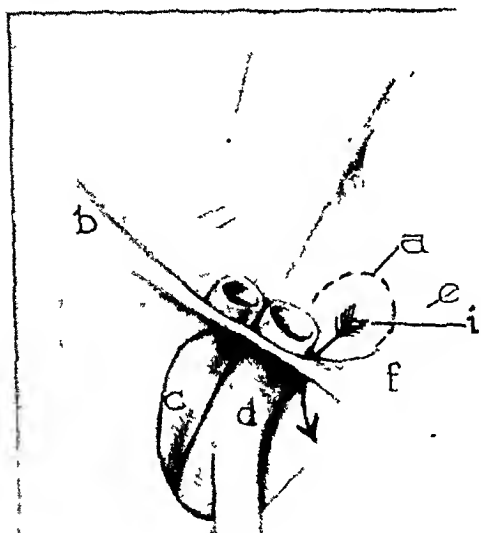


FIG. 4

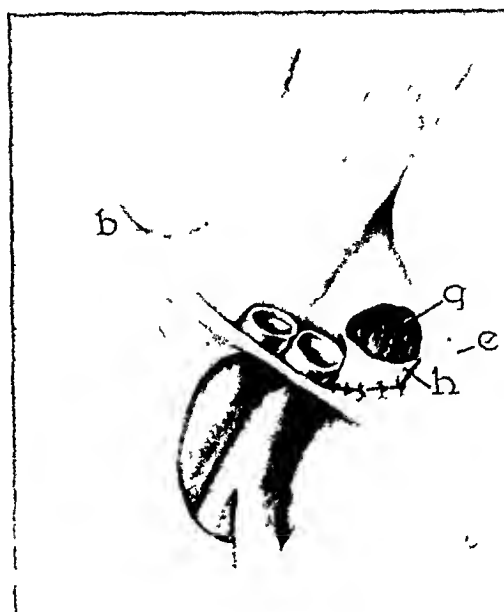


FIG. 5

FIGS. 4, 5—Drawings of anterio-posterior view to show the method of using pectineus fascia to close the femoral canal.

- a. Incision into pectineus fascia
- b. Poupart's ligament
- c. Femoral A
- d. Femoral V
- e. Cooper's ligament covering pectineal line
- f. Gimbernat's ligament
- g. Pectineal muscle
- h. Flap of pectineal fascia
- i. Femoral canal

usually small gut or omentum or both, the peritoneum is pushed through the space medial to the femoral vein and lateral to Gimbernat's (lacunar) ligament. Anteriorly, lie Poupart's ligament and transversalis fascia and posteriorly, the pectineus fascia and Cooper's ligament. Such a canal, when fully developed, is approximately  $\frac{3}{4}$  inch in length and extends from the femoral ring above to the fossa ovalis below.

Poupart's ligament, as is well known, is a strong fibrous band extending from the anterior superior spine of the ilium to the pubic tubercle and is continuous with the aponeurosis of the external oblique muscle above. Medially near the attachment of the ligament to the pubic tubercle, diverging fibers are given off which pass inward and upward to the pectineal line, thus giving rise to Gimbernat's ligament.

Cooper's ligament is a strong fibrous band which is continuous with Gim-

bernat's ligament and extends laterally along the pectineal line to which it is attached. It is strengthened by and continuous with the pectineal fascia which overlies the pectineus muscle. From anatomic dissection and from observation of the attachments of these ligaments to the pelvic bones, it is evident that Cooper's ligament occupies a plane proximal to Poupart's ligament and this becomes more pronounced as the pectineal line swings laterally. This fact permits a flap of pectineus fascia to be dissected up and sutured to Poupart's ligament without tension (Figs. 4, 5).

Transversalis fascia, when well developed, is a tough fibrous structure which lies just superficial to the peritoneum and through which both direct and indirect inguinal hernias, as well as femoral, must pass. Needless to say, such hernias cannot develop so long as this fascia remains intact. It is an extremely valuable tissue for use in the repair of these hernias when well developed but it is frequently found to be an entirely inadequate structure.

The aponeurosis of the external oblique muscle is attached to the superior margin of Poupart's ligament throughout its entire length. In the majority of instances, it is a well developed, tough, fibrous structure and is easily mobilized over a wide area so that usually it can easily be brought down to Cooper's ligament without tension. When well developed, it is valuable in the repair of both inguinal and femoral hernias but it also frequently is such an attenuated structure as to be of little value.

#### THE OPERATION

It is necessary to make the inguinal type of exposure if the method to be described is used.

An incision is made parallel to and slightly above Poupart's ligament, two thirds of the distance from the pubic spine to the anterior-superior spine of the ilium. The aponeurosis of the external oblique muscle is incised just above Poupart's ligament. The cord, or round ligament, is retracted out of the way. The neck of the femoral sac is freed, the sac opened and contents, if any, reduced. The sac is then dissected from the femoral canal, ligated high and excised. The femoral vessels are then retracted laterally. The pectineus fascia and Cooper's ligament are cleansed of attached cellular tissue. An incision is made into the pectineus fascia to include Cooper's ligament and a flap of these structures fashioned sufficiently large to cover over the femoral canal and to permit its being sutured to the inner side of Poupart's ligament without tension (Fig. 1, 5). It is surprising how easy it is to obtain such a flap and what an adequate structure it proves to be in most instances. None of the pectineus muscle is included. A search is made for the transversalis fascia and when found it is carefully dissected out and mobilized and sutured to the inner side of the flap of the pectineus fascia and laterally to Poupart's ligament along with the aponeurosis of the external oblique muscle. The lower edge of the external oblique aponeurosis attached to Poupart's ligament is sutured to the adjacent fascia as illustrated in the accompanying diagrams. This repair adequately deals with the femoral hernia and takes care of the

potential formation of an inguinal hernia that might result from such an incision.

This type of repair has been found to be particularly advantageous when it has been found necessary to sever Poupart's ligament to reduce strangulated gut when severing Gimbernat's ligament did not give adequate enlargement to the entrance to the femoral canal. Interrupted silk or cotton sutures are used throughout the repair.

#### ADVANTAGES OF THE OPERATION AS DESCRIBED

As has been pointed out, it is my belief that in addition to the removal of the sac in femoral hernia an attempt should be made to either obliterate the femoral canal or close off the proximal femoral opening in order to minimize recurrences. Utilization of the transversalis fascia or the aponeurosis of the external oblique muscle serves this purpose well when these structures are well developed and when they can be sufficiently mobilized to be sutured to Cooper's ligament without tension. With sufficient mobilization of these structures this can usually be accomplished.

Pectineus fascia, on the other hand, is readily accessible with a minimum of dissection necessary for its mobilization. It is a well developed structure and it can be sutured to Poupart's ligament without tension; or, at least, such has been the case in those individuals subjected to operation and in dissections on the cadaver, with one exception, in which case the fascia was very poorly developed.

It is well in dealing with hernias to have in mind several alternate procedures, for it has been everyone's experience that certain structures for the repair of hernia may be well developed in one individual and utterly lacking or attenuated in others. In other words, fit the operation to the individual and not the individual to the operation.

This presentation has the same fallacies as most discussions on the subject. The method has not been used sufficiently often nor results observed over a sufficiently long period of time to arrive at definite conclusions. In my experience with 606 hernia repairs of all kinds, 20 were for femoral hernia. Five of these were repaired by the technic described. However, the method appears to be anatomically sound and I believe wider use will substantiate this belief.

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# RESULTS OF TREATMENT OF PERFORATION OF THE ESOPHAGUS\*

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FROM 1925 THROUGH 1947, 69 cases of peri-esophageal infection following perforation of the esophagus by instrumentation, foreign body, or both were encountered at the Mount Sinai Hospital, New York City. The results in the first 40 of these (to mid-1941) have already been published by Neuhof and Jemerin. However, as the number of cases in the original report has subsequently been augmented by almost 75 per cent, and as the factor of chemotherapy must now also be evaluated, an inclusive report at this time seems pertinent.

Of the 69 patients, 44 recovered and 25 died, a gross mortality of 36.2 per cent. Our interest, however, lies in the results of treatment, and gross mortality is therefore meaningless. The important thing is to determine whether, with the passage of years, results have improved. If so, can this improvement be correlated with a better understanding of the sequelae of perforation and with methods of treatment? In Table I the cases are tabulated according to years.

From the table, it is readily seen that definite progress has been made. Dividing the cases into two groups, those prior to 1936 and those since, the progress is even more apparent. For, of the 22 patients from 1925 through 1935, 17 died, a mortality of 77.3 per cent, while of the 47 patients since 1936, only eight died, a mortality of 17.0 per cent. The reason for selecting 1936 as the dividing point is not arbitrary and will be apparent later.

To what is this striking difference in mortality attributable? In part, the answer is supplied by further dividing the cases into those operated upon and those treated conservatively. Sixteen patients were not operated upon. Of these, 11, or 68.7 per cent died. Fifty-three patients had definitive operative procedures directed toward the lesion produced by the perforation as distinct from palliative procedures such as gastrostomy or tracheotomy. Fourteen, or 26.4 per cent of these died. By breaking down the material further into a chronologic listing of the operative and non-operative cases, additional information is obtained in Table II.

It is now seen why 1936 has been selected as the dividing point. At about this time, surgery began to be recognized as the treatment of choice. Prior to this date, only 50 per cent of the cases were treated surgically, while about 90 per cent have been accorded its benefits since. Thus, the improvement in results has paralleled the increased utilization of surgical therapy. However, other factors must certainly have been at play also as the results for surgical therapy itself have improved markedly. This is shown by the reduction in

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mortality for surgically treated cases from 72.7 per cent before 1936 to 14.3 per cent since that date.

The most important single factor instrumental in recovery is the recognition of esophageal perforation as a surgical lesion. The next most important is realization of the need for prompt intervention. From its inception, peri-esophageal infection following esophageal perforation is almost always diffuse and intense in nature. This is because usually the bacteria are

TABLE I.—*Cases of Esophageal Perforation.*  
*Chronologic Listing of Recoveries and Deaths.*

Year	No. of Cases	Recoveries	Deaths
1925	1	0	1
1927	2	1	1
1928	1	1	0
1929	1	0	1
1930	4	0	4
1931	6	1	5
1932	2	1	1
1933	2	0	2
1934	1	0	1
1935	2	1	1
1936	5	4	1
1938	6	5	1
1939	5	2	3
1940	3	3	0
1941	7	6	1
1942	2	1	1
1944	4	3	1
1945	4	4	0
1946	7	7	0
1947	4	4	0
	69	44	25
			Gross mortality 36.2%
Cases prior to 1936:	22	5	17
			Mortality 77.3%
Cases since 1936:	47	39	8
			Mortality 17.0%

anerobic and because they are introduced too suddenly for local defenses to be mobilized. Prompt destruction of tissue with liquefaction resulting in rapid abscess formation usually occurs and the process is not infrequently putrid or gangrenous. But a wide zone of cellular inflammation remains surrounding the abscess. If the inflammation is not checked by drainage or other means, this serves as a zone of spread for a mediastinal phlegmon or cellulitis which was almost always the common denominator in the fatal cases.

Obviously, it is not the perforation *per se* which kills but the infection which spreads in the highly cellular cervico-mediastinal planes. Thus, in the usual case, drainage must be prompt and adequate in order for it to have its greatest chance. Analysis of the case material indicates that in early years operation was performed reluctantly, almost as a last resort measure, while in recent years prompt drainage has been the rule. Prior to 1936, in only three

# PERFORATION OF THE ESOPHAGUS

of the 11 surgically treated cases was operation performed less than one week after the perforation had occurred. Since 1936, 35 of the 42 treated surgically were operated upon less than a week after perforation and 20 of these were operated upon within two days.

TABLE II.—*Cases of Esophageal Perforation.*  
*Chronologic Listing of Operative and Non-Operative Recoveries and Deaths.*

Year	No. of Cases	Operated			Non-Operated			
		No.	Recovered	Died	No.	Recovered	Died	
1925	1	1	0	1	0	0	0	
1927	2	0	0	0	2	1	1	
1928	1	0	0	0	1	1	0	
1929	1	1	0	1	0	0	0	
1930	4	2	0	2	2	0	2	
1931	6	3	1	2	3	0	3	
1932	2	2	1	1	0	0	0	
1933	2	1	0	1	1	0	1	
1934	1	0	0	0	1	0	1	
1935	2	1	1	0	1	0	1	
1936	5	4	4	0	1	0	1	
1938	6	6	5	1	0	0	0	
1939	5	5	2	3	0	0	0	
1940	3	3	3	0	0	0	0	
1941	7	7	6	1	0	0	0	
1942	2	2	1	1	0	0	0	
1944	4	3	3	0	1	0	1	
1945	4	4	4	0	0	0	0	
1946	7	4	4	0	3	3	0	
1947	4	4	4	0	0	0	0	
		69	53	39	14	16	5	11
		Operative Mortality 26.4%			Non-operative Mortality 68.7%			
Cases prior to 1936: 50% treated surgically; only 3 out of 11 operated upon less than 1 week after perforation.								
		22	11	3	8	11	2	9
		Operative Mortality 72.7%			Non-operative Mortality 81.8%			
Cases since 1936: 89.4% treated surgically; 35 out of 42 cases operated upon less than 1 week after perforation; 20 cases operated upon less than 2 days after perforation.								
		47	42	36	6	5	3	2
		Operative Mortality 14.3%			Non-operative Mortality 40.0%*			

\* This figure does not include many non-operative failures whose lives were saved by late surgical intervention (see text).

Ideally, operation is performed immediately upon recognition of the existence of a traumatic laceration of the esophagus and certainly before infection has descended into or become full blown in the mediastinum. Such an operation can be regarded in the nature of a prophylactic measure. However, this is not always possible. Many cases arrive only a considerable time after the accident has occurred. Fortunately deterioration is not always rapid. When

the perforating agent has been a small foreign body such as a fish bone, the resulting infection may be less virulent and develop much more slowly than after a large tear by an instrument. Also, not infrequently the process has been delayed by the spontaneous establishment of partial drainage by perforation of the abscess into the esophagus or lung. But one has only to contrast the satisfactory results of early operation with the disastrous results of non-intervention or late operation to realize that perforation of the esophagus provides an urgent indication for operation whenever possible.

Operation in itself accounts for practically no mortality. Perforation usually takes place at the junction of the pharynx with the esophagus and accordingly, in most cases, cervico-mediastinal drainage effected through the neck under local anesthesia is sufficient to take care of the lesion. The technic, patterned after Marschik, is simple and well standardized. It is described in detail by Neuhof and Jemerin. The operation was performed in 41 of the 53 patients in our series that were operated upon and only in three cases was it necessary to supplement the procedure by a subsequent posterior mediastinotomy. Of the remaining 12 operative cases, primary posterior mediastinotomy was performed in three because of the location of the lesion, and thoracotomy with drainage of mediastinal and complicating lung abscess or empyema was performed in the other nine. Needless to say, appropriate supportive measures to achieve optimum general condition are an integral part of the surgery.

Analysis of the deaths in the operative cases before 1936 shows that these were due for the most part to spread of infection because of too long delayed or improperly conceived operation. The characteristic mode of spread in these fatal cases was as mediastinal phlegmon. Since 1936, the six deaths following surgery were due to secondary hemorrhage from major vessels in two cases, cardiovascular collapse in one case in which the true nature of the basic condition was not recognized until the patient was in extremis, delayed poorly conceived operation in one case, and overwhelming infection in one case not admitted until ten days after perforation.

The non-operated patients died, of course, of undrained infection. One of the two patients since 1936 was admitted in extremis with infection already spread throughout the mediastinum. In the other, the course of events following esophagoscopy was not recognized as the sequelae to an esophageal perforation and death ensued despite sulfadiazine and penicillin.

The recent availability of various potent chemotherapeutic agents again raises the question of conservative therapy. Actually, it must be recognized that an effort was made to treat conservatively many cases that came to operation, or at least to observe them for a sufficient period to determine whether they would resolve without operation. Thus the 53 operative cases include 40 in which there was a preliminary period of waiting of at least two days (either before or after they were admitted), and 25 in which the period of temporization was at least five days. The longest interval before operation was 10½ months in a case of mediastinal abscess which had perforated into the lung. Since 1939 most of these cases have had chemotherapy, the sulfona-

mides prior to 1944 and penicillin with or without the sulfonamides since 1944. The course seemed to be in no way influenced by the sulfonamides but in 1946, three patients recovered with penicillin therapy. However, one died which would otherwise have been saved and five other patients with preliminary penicillin for five, three, one, nine, and two days, respectively, deteriorated while under treatment and required surgery. One of these deteriorated so rapidly despite penicillin that in two days she was almost moribund and her recovery after operation was a surprise. Another was discharged apparently well after five days of penicillin only to return a week later with an abscess that required drainage. The three patients who recovered with penicillin alone were apparently minor perforations with only minimal peri-esophageal contamination. Thus it is seen that the failures with non-operative therapy are not given by the mortality figures alone. The mortality under conservative therapy including the antibiotics would have been much higher had not many of these cases been taken out of that category and saved by operative intervention.

Streptomycin has not had an adequate trial but our impression is that in esophageal perforation no chemotherapeutic agent is as yet a substitute for prompt drainage, particularly since we are dealing with anerobic infection in a closed space and an operative procedure in itself so little hazardous. Only potential harm can be caused by waiting, and, in general, the more prompt the operation, the greater the chance for recovery. Actually, mortality from esophageal perforation should be rare, occurring only in unpreventable situations such as a patient admitted with too widespread an infection late after perforation, fulminating infection following extensive laceration of the esophagus, and serious complicating lesions.

#### SUMMARY

1. The results in 69 cases of esophageal perforation covering a period from 1925 through 1947 are presented.
2. Chronological listing of the results shows a marked improvement with the passage of the years.
3. Further breakdown into operative and non-operative cases shows the improvement to be due to an increased incidence of prompt surgical intervention.
4. Penicillin and the other chemotherapeutic agents should be used only as an adjunct to prompt surgery.

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# TREATMENT OF PANCREATIC CYSTS\*†

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PANCREATIC CYSTS may be of the proliferative or the non-proliferative type. Though the literature is scant, most proliferative cysts reported have been malignant.<sup>1</sup> Extirpation of this type of cyst is the treatment of choice because it represents a precancerous lesion. Nonproliferative cysts, on the other hand, rarely if ever undergo malignant degeneration and therefore can be treated in one of several ways. Extirpation should be employed if the cyst can be easily enucleated. If the cyst is fused intimately with surrounding structures, its removal might prove hazardous and increase unnecessarily the mortality rate. In the past, marsupialization has been employed. Gussenbauer<sup>2</sup> in 1883 performed the first external drainage of a pancreatic cyst. Judd<sup>3</sup> reported 33 cases of marsupialization, many of which were followed by sinus tracts that persisted for two years. Kerr<sup>4</sup> had a patient who drained for 15 years. The objections to this form of therapy are autodigestion of the abdominal wall, infection of the cyst and sinus tracts, severe inanition and repeated hemorrhages. Attempts to close these fistulae by irradiation,<sup>5</sup> radium,<sup>6</sup> and sclerosing agents<sup>7</sup> have not proven efficacious. Marsupialization should have little place in our present surgical armamentarium.

Another therapeutic approach, which has an increasing number of proponents, is the performance of an anastomosis between the cyst and a hollow viscus. The first anastomosis was performed by Jedlicka,<sup>8</sup> between the cyst and stomach. Anastomoses between the cyst and the gallbladder have been reported by Waltzel<sup>9</sup> and Neuffer<sup>10</sup> with variable results. Failures have occurred probably because of contamination of the cyst by bacteria and intestinal contents.

Recently Adams<sup>11</sup> reported two cases of anastomosis between the jejunum and pancreatic cyst with an auxiliary jejuno-jejunostomy. Both these patients had satisfactory convalescences which he attributed to successful shunting of the jejunal contents away from the lumen of the cyst. To increase the likelihood of this diversion, a Roux-en-Y anastomosis was performed in one of our cases.

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**Case 1.**—A. P., a 27-year-old white male, entered the hospital on April 11, 1947, complaining of severe left lower quadrant and para-umbilical pain. Twenty-eight hours before admission he first became aware of para-umbilical pain which radiated to the left lower quadrant. Although the pain was constant, there were occasional severe colicky attacks. There was no nausea, vomiting, diarrhea or melena. The urinary tract was negative.

Examination revealed an acutely sick male lying with his thighs maintained in flexion. Temperature was 99° F., pulse 92 and respirations 20. The abdomen was scaphoid. Marked tenderness and spasm were elicited over the left rectus abdominis muscle. Hyperperistalsis was present. Rectal examination was uninformative. The white blood cell count was 15,400. The differential smear was normal. Serum amylase was 8 units (normal 8-64 units.) Intravenous pyelography revealed a displacement of the left ureter toward the midline, obliteration of the left psoas shadow and probable indentation of the lesser curvature of the stomach. The patient's symptoms became more severe and three hours after admission laparotomy was performed.

*Operation:* The abdomen was opened through a left rectus muscle-splitting incision. A large pancreatic cyst was found lying in the lesser omental cavity with a thumb-like projection that protruded behind the stomach through the gastrohepatic omentum. This projection was markedly hyperemic and covered with fresh fibrin. There was no evidence of fat necrosis or free fluid in the abdomen. After exposing the cyst through the gastrocolic ligament, the finger-like projection was freed from the gastrohepatic omentum and was excised. A large amount of necrotic debris and serosanguineous fluid was evacuated from the cyst which comprised the entire body and tail of the pancreas. Because the cyst was firmly adherent to the base of the transverse mesocolon, the splenic vessels and the posterior wall of the stomach, extirpation was deemed unwise. The jejunum was then divided about 10 inches from the ligament of Treitz. The aboral end was delivered through an opening in the mesocolon and was anastomosed to the dome of the cyst with a two-layer technique. The oral end of the jejunum was anastomosed to the distal loop about 6 inches from the cysto-jejunostomy in the manner of Roux.

The fluid evacuated from the cyst was found to contain pancreatic ferments and a pathological diagnosis of pseudocyst of the pancreas was made.

*Clinical course.* The patient made an uneventful convalescence. A gastro-intestinal series on the 12th postoperative day revealed a normal intestinal pattern. There was no filling of the cyst cavity. The patient was discharged on the 14th postoperative day. A gastro-intestinal series taken two and six months postoperatively revealed no abnormalities. He has continued to be asymptomatic.

#### COMMENT

Although the follow-up of this patient has been short, the advantages of an internal anastomosis over marsupialization are evident in the patient's asymptomatic convalescence. The anastomosis en-Y should prove more effective than a cysto-jejunostomy in continuity, by virtue of side-tracking the intestinal content away from the cyst.

**Case 2.**—R. L. D., a 54-year-old male, entered the hospital for the fifth time on April 1, 1947, complaining of nausea and vomiting of two months' duration.

He was first admitted to the hospital in December 1941, because of episodes of gastric distress, pain and flatulence. After the gastro-intestinal and gallbladder series were reported negative, he was discharged. He returned in September 1942, because of weakness, weight loss and jaundice. On October 17, 1942, a laparotomy revealed a large cyst of the head of the pancreas which was drained externally. In March, 1944, he entered the hospital for the third time because of persistent drainage from the sinus tract. Surgical excision of the cyst and sinus tract was attempted, but the surgeon was unable to remove

the cyst in toto. A new sinus developed postoperatively and continued to drain after he left the hospital. This sinus tract closed spontaneously in January, 1945. In March, 1945, he entered again and an incisional hernia was successfully repaired.

He felt well until February, 1947, when he began to have nausea and vomiting which became progressively worse. He entered another hospital where he was treated conservatively for intestinal obstruction for 20 days. He left the hospital only to return four days later with the same complaints. After a few days he was symptomatically better and was discharged. Forty-eight hours later, his symptoms recurred and he entered the hospital on April 1, 1947, with a diagnosis of intestinal obstruction.

Physical examination revealed a thin, undernourished, slightly jaundiced, chronically ill male. A mass the size of a large orange, which appeared to be firmly adherent to the deep structures, was felt in the epigastrium. The red blood cell count was 3,600,000; hemoglobin 12 Gm.; white blood cell count 10,000 with 79 per cent neutrophils. The icterus index was 28. Roentgenograms of the chest revealed a right apical opacity which had increased in size since previous roentgenograms taken in 1941. There was also an increase in the number and size of emphysematous blebs in the right lung since 1941. Sputum and gastric examinations revealed no acid fast bacilli.

Because of the persistence of jaundice and the patient's downhill course, laparotomy was performed on April 19, 1947, through a transverse upper abdominal incision dividing both recti. A large cyst, measuring 10 cm. in diameter, was found involving the head and body of the pancreas. The gallbladder was tense, appeared normal, but could not be emptied by manual compression. The cyst was exposed and opened. After draining the amber colored fluid, a line of cleavage was finally established between the cyst wall and capsule. The cyst was removed completely. The gallbladder was then easily compressible and was emptied. It was inferred that extirpation of the cyst relieved compression of the common duct. No injury to the common duct was noted. A rubber Penrose drain was left in the lesser omental cavity and the abdomen closed in layers.

The fluid from the cyst contained pancreatic ferments. The pathological diagnosis was cyst of the pancreas, either retention or pseudocyst.

*Clinical course.* On the first postoperative day the patient had a spontaneous pneumothorax, and at this time tubercle bacilli were found in the sputum. Pneumothorax was continued with weekly refills.

On the fourth postoperative day, biliary drainage was noted from the operative wound. Stools became clay colored. Lipiodol injected into the fistula entered the duodenum. Patient continued to have epigastric distress relieved on occasion by probing the sinus tract with a release of bile-stained material and a concomitant diminution in the icterus index. On May 12, 1947, a catheter was inserted into the sinus tract. Diodrast outlined the entire biliary tree and the catheter appeared to be in the common duct. Patient was prepared for further surgery.

The second exploration was accomplished on July 7, 1947, with the catheter still in the common duct. A side-to-side choledochoduodenostomy, as advocated by Sanders,<sup>12</sup> was performed. A T-tube was inserted into the common duct above the site of the anastomosis. This was brought out through a separate stab wound in the flank.

The postoperative course was uncomplicated. On the 36th postoperative day, the T-tube was removed after repeated lipiodol injections revealed the dye entering the duodenum. The original sinus wound drained less and less bile-stained material, and finally closed. The icterus index became normal. He had no complaints when last examined in October, 1948. The pneumothorax refills have been continued without incident.

#### COMMENT

This patient with a long history of a pancreatic cyst and draining fistulae underwent extirpation of the cyst. Unfortunately, a biliary fistula developed, which required further surgery. Since bile was not noted on the dressing

until the third postoperative day, it is probable that the lower part of the common duct damaged by the previous compression of the duct by the cyst had been eroded by the pancreatic ferments postoperatively. In retrospect, an anastomosis en-Y, as described in Case I, would have been preferable.

#### DISCUSSION

The incidence of carcinoma associated with proliferative pancreatic cysts is so high that the complete excision of these cysts should be performed. In the treatment of the non-proliferative type of pancreatic cyst, the decision is less clear cut. Marsupialization in general is a poor operation because of its many untoward sequelae: erosion of the skin, infection of the sinus tract, and failure of the fistula to heal. The operation of choice is either an internal anastomosis between the cyst and the jejunum or the extirpation of the cyst wall. The latter procedure should be performed whenever possible, but it is contraindicated when its employment might jeopardize the integrity of important contiguous structures. If jaundice is present preoperatively as in Case 2, excision of the cyst is unsafe because of the high incidence of injury to the common duct, either at the time of operation or by enzymatic erosion postoperatively. Carter and Slattery<sup>13</sup> reported injuring the common duct in two of the five cases treated by excision of the cyst. The rent in the duct was closed and a T-tube inserted into the common duct proximally. These patients had a satisfactory but protracted convalescence. An internal anastomosis between the cyst and jejunum is a safer procedure in the complicated case. The morbidity and mortality for this operation cannot be properly adduced until a much larger series is compiled. The results thus far have been so gratifying that employment of this procedure seems warranted. Infection of the cyst wall should be a less frequent complication, if the intestinal stream is shunted away from the cyst by the performance of a cysto-jejunostomy en-Y rather than by anastomosing those two structures in continuity.

#### SUMMARY

1. Two cases of non-proliferative cysts of the pancreas have been operated upon successfully.
2. One was treated by excision of the wall, the other by an anastomosis between the cyst and the jejunum en-Y (Roux).
3. Non-proliferative cysts involving the head of the pancreas should not be extirpated because of the high incidence of injury to common bile and pancreatic ducts.
4. This is the first report of the successful application of the Roux type of anastomosis to the treatment of pancreatic cysts.

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## BOOK REVIEW

ATLAS OF PLASTIC SURGERY, BY M. I. BERSON, M.D.,  
NEW YORK CITY, GRUNE & STRATTON, INC.—1948

In his "Atlas of Plastic Surgery" Berson presents graphically standard methods and technics in reparative surgery. The normal anatomy and common types of deformity are depicted in line drawings and photographs. Necessary instruments and consecutive steps for repair of these deformities are likewise illustrated by photographs, drawings, and an accompanying explanatory text.

In the eight chapters into which the Atlas is subdivided, that dealing with the nose is by far the most complete and most valuable. It is recommended to any who are uncertain of indications for the several technics of corrective rhinoplasty. The presentation is simple and direct and shows an appreciation by the author of the methods, problems and pitfalls in this procedure. The chapters on the ear, eyelids and lips are likewise well done and most of the corrective technics for minor deformities of these structures are graphically presented. The operation of "face-lifting," and some of the technics of mammaplasty and lipectomy are presented in some detail. The Mirault operation for single harelip and the Federspiel operation for double harelip are shown. The methods presented for cleft palate repair are taken from the writings of Dorrance and Bransfield. The securing and use of fascia, bone, and cartilage transplants for deformities of the face are illustrated.

The very important matter of skin transplantation, both as pedicle flaps and as free grafts, is disappointingly inadequate. The author does present the Z-plastic procedure, which lends itself to illustration. Various types of skin suture and repair are shown, including closure by the somewhat time-worn impractical geometrical patterns that have been passed down from generation to generation of plastic surgeons.

For those surgeons desiring a better understanding of cosmetic plastic surgery of the face and particularly of the nose, lips, and ears, this Atlas will prove of real value. It will not be helpful, however, to those interested in general plastic surgery of massive and complicated repairs of the face and jaws and of reparative surgery of the extremities.

—BRADFORD CANNON, M.D.

# PANCREATIC PSEUDOCYSTS: REPORT OF A CASE TREATED BY CYSTOGASTROSTOMY\*†

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PSEUDOCYSTS OF THE PANCREAS are not true neoplasms but are collections of pancreatic secretions in the lesser peritoneal sac. They have no epithelial lining, their walls being formed by the peritoneum of the lesser sac. These collections usually present between the stomach and transverse colon, beneath the gastrocolic omentum, although they may present between the stomach and liver or between the leaves of the transverse mesocolon. Most pseudocysts follow an attack of acute pancreatitis or pancreatic necrosis, although cases have been reported following upper abdominal trauma. The interval between the original episode of pancreatitis and the clinical manifestations of the cyst is usually several weeks.

The diagnosis of pancreatic pseudocyst is usually made by roentgenologic studies after the finding of a mass in the upper abdomen developing a few weeks after an attack of acute pancreatitis. A most significant finding is distortion of the gastric or duodenal outlines by an extrinsic mass seen after the ingestion of a barium meal. Cysts in the body of the pancreas will cause indentation of the greater curvature of the stomach and downward displacement of the transverse colon and duodeno-jejunal junction. Cysts in the region of the head of the pancreas may cause widening of the duodenal loop. Intravenous urograms may show impaired function of the left kidney and incomplete filling of the left renal pelvis. These findings may be due to the pressure of the cyst on the renal vessels.<sup>1</sup>

Pseudocysts usually contain turbid fluid which may be hemorrhagic. Shreds of necrotic pancreatic tissue may be present. Bacterial contamination is common and is frequently due to colon organisms. High amylase readings from examined fluid prove its pancreatic origin.<sup>2</sup>

Excision of pancreatic pseudocysts has proved difficult, if not impossible, and has been attended by a high mortality. As a result the accepted treatment has been evacuation of the contents and marsupialization of the sac. This procedure is followed by prolonged drainage, skin excoriation, loss of fluid and electrolytes and the occasional necessity of secondary operations to close the persistent pancreatic fistula which develops in some cases. In attempting to overcome these undesirable sequelae of marsupialization various methods of internal drainage have been devised.

Internal drainage by anastomosis of the cyst to some portion of the gastro-intestinal tract has been done successfully several times. The procedures in which good results have been reported are cystojejunostomy and cystogas-

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FIG. 1.—X-ray of stomach in prone position showing marked distortion and displacement of greater curvature. Taken January 28, 1947.



FIG. 2.—X-ray of colon taken on January 28, 1947 showing downward displacement of splenic flexure.

trostomy. In 1943 Chesterman<sup>3</sup> reported a successful case of cystojejunostomy. Adams and Nishijima<sup>4</sup> in 1946 reported two cystojejunostomies done at the Lahey Clinic with good results. The first recorded successful cystogastrostomy was done by Jedlicka in 1923.<sup>5</sup> In 1931 Jurasz<sup>6</sup> reported two cases done by incising the anterior wall of the stomach, making a cautery opening through the posterior wall of the stomach into the cyst and closing the anterior gastrotomy. Harries,<sup>7</sup> in 1934 reported a successful cystogastrostomy. Brocq and Aboulker<sup>8</sup> in 1940, reviewed the literature and found 17 cases in which internal drainage of pancreatic pseudocysts had been done, including cystogas-



FIG. 3.—Taken on March 3, 1947. Arrow points to barium in remaining cyst cavity.

trostomies, cystoduodenostomies, cystocholecystostomies and cystojejunostomies. These included the cases of Jedlicka, Jurasz and Harries. Mahadevan<sup>9</sup> in 1943 reported a case in which the anastomosis was done between the posterior gastric wall and the cyst, after doing an anterior gastrotomy. dos Santos<sup>10</sup> in 1944 reported a similar case. The case report which follows is one in which two separate pseudocysts developed in a female patient, one of which was treated by marsupialization, the other by cystogastrostomy.

#### CASE REPORT

M. H., white female, age 55, entered Jefferson Hospital, Philadelphia, on January 25, 1947, complaining of pain in the left flank, nausea and vomiting. She gave a history of an attack of vague abdominal pain beginning on December 15, 1946, followed the next



day by chills, fever, nausea, vomiting and severe epigastric pain radiating to the left shoulder. These symptoms continued with diminishing intensity for 4 days. She did not have medical attention during this time. On January 15, 1947 she began to have nausea and vomiting again. Since January 22nd she had excruciating abdominal pain, pain in the left loin and flank, chills and fever. She had no urinary symptoms or change in bowel habit.

*Physical examination* showed a pale, apprehensive, middle-aged female in obvious discomfort. There was marked left-sided abdominal rigidity and tenderness. It was difficult to be sure because of the rigidity but it was felt that there was a mass in the left upper abdomen. No jaundice was present. The white blood cell count on the day of admission was 10,400. Urine obtained by catheterization was loaded with red blood cells. The temperature at this time was 101.4. An intravenous urogram done on January 26,



FIG. 4.—Taken on April 3, 1947. Arrow points to fleck of barium which represents final cyst remnant.

1947 showed incomplete filling of the left renal pelvis and ureter. Cystoscopy was done on January 27, 1947. Clear urine was obtained from the left kidney. A retrograde pyelogram showed a left bifid renal pelvis but was otherwise normal. The roentgenologist reported that there was no evidence of intrinsic renal disease but that a perinephric abscess might be present. The patient was seen on January 27, 1947 by Dr. D. M. Davis whose opinion was that there was no renal or perirenal disease to account for her symptoms. On January 28, 1947 a barium meal and barium enema were given. Roentgenograms showed a mass in the left upper abdominal quadrant displacing the stomach forward and to the right (Fig. 1) and the splenic flexure downward (Fig. 2). A chest roentgenogram showed a small amount of fluid in the left pleural cavity. The tentative diagnosis of pseudocyst of the pancreas was strongly confirmed by the roentgenologic findings. A serum amylase done on January 28, 1947 was reported as 800 units. The patient was prepared and operation was carried out on January 29, 1947. The abdomen was opened through a left upper transverse incision and a large pancreatic pseudocyst was found presenting through the gastrocolic omentum. Many small areas of fat necrosis

## PANCREATIC PSEUDOCYSTS

were seen in the omentum. The cyst was aspirated and about 2 liters of straw-colored fluid containing particles of necrotic tissue were removed. The interior of the cyst was explored digitally and no loculations found. The cyst was attached to the mid portion of the pancreas. The cyst was marsupialized and the incision closed. An amylase reading from the aspirated fluid was 64,000 units. Following operation there was a large amount of drainage which was severely irritating to the surrounding skin. Difficulty was encountered postoperatively in maintaining normal fluid and electrolyte balance and in spite of intensive care the carbon dioxide combining power and plasma chlorides tended to remain low. On February 8, 1947 an ovoid mass was felt in the right upper abdominal quadrant. Clinical jaundice was noted on February 17, 1947. On February 18, 1947 the patient was operated upon again. A right upper rectus incision was made and a large pancreatic pseudocyst was found in the region of the head of the pancreas. This was making extrinsic pressure on the duodenum and the retroduodenal portion of the common bile duct. The gallbladder contained many calculi. The cyst presented through the gastrocolic omentum and was densely adherent to the posterior wall of the stomach. The common bile duct was markedly dilated. The cyst was aspirated and contained a thick brown fluid which upon culture showed growth of colon bacilli. The old transverse incision was then opened and digital exploration of the cyst and the old pancreatic fistula carried out simultaneously. No communication could be demonstrated between the two. Cholecystectomy was then done and the common duct was opened. Catheters and dilators passed freely into the duodenum and it was felt that the common duct obstruction had been due entirely to extrinsic pressure. A T-tube was placed in the common duct. A two layer anastomosis was then done between the cyst and the stomach, the anastomosis being placed on the greater curvature close to the pylorus. The incision was closed and the patient returned to her room in good condition. The jaundice had subsided completely the following day. In the next 2 weeks the patient improved greatly. Biliary drainage gradually decreased. Drainage from the old pancreatic fistula stopped almost entirely. On March 3, 1947 a cholangiogram showed immediate entrance of the dye into the duodenum and normal filling of the hepatic radicals (Fig. 3). A barium meal was then given which showed normal gastric emptying and a persistent shadow below the pylorus suggesting barium in the remnant of the cyst (Fig. 3). The patient was sent home on March 11, 1947 with the T-tube clamped. She was readmitted for study on April 1, 1947. Her general condition was excellent and she had no symptoms. There was no external biliary or pancreatic drainage. Her serum amylase at this time was 80 units. A barium enema on April 1, 1947 showed no displacement of the colon. A cholangiogram showed no obstruction to the entrance of the dye into the duodenum. Roentgenograms taken after a barium meal on April 3, 1947 showed a fleck of barium below the pylorus which was interpreted as being the last small remnant of the cyst (Fig. 4). Gastric analysis on April 5, 1947 showed normal values for free and total acid and an amylase of less than 80 units. Fasting blood sugar was 93 mg/100 cc. The T-tube was removed on April 5, 1947 and the patient was discharged. She has gained weight and has been symptom free up to the present time. Her incisions are well healed and there is no external biliary or pancreatic drainage.

### SUMMARY

This case is reported because of the rarity of the development of two pancreatic pseudocysts in one patient and to demonstrate the successful use of a method of treatment of pancreatic pseudocysts which has been used very seldom in the past.

We believe that the method of anastomosis used is practical and can be applied in any case in which the cyst wall is firm enough to permit careful suturing. The major appeal of this method is the avoidance of prolonged

drainage, skin excoriation, fluid and electrolyte loss and secondary operations for the closure of fistulae which may follow upon marsupialization.

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# ORAL STREPTOMYCIN IN SURGERY OF THE LARGE BOWEL:

## The Production of Secondary Hypoprothrombinemia\*

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STREPTOMYCIN, administered orally, is being employed with increasing frequency in several clinics in the preparation of the large bowel for surgery.<sup>10, 12, 18</sup> The superiority of this antibiotic over the sulfonamides, sulfathalidine and sulfasuxidine, previously employed in the reduction of the bacterial flora of the large intestine was established by Ravdin and his co-workers.<sup>10</sup>

It has been suggested that in the course of diminishing the bacterial population of the colon, sulfasuxidine and sulfathalidine interfere with the synthesis of an anti-hemorrhagic factor, probably vitamin K. Sanders and Halperin<sup>13</sup> have reported postoperative hemorrhage in two patients prepared with oral sulfasuxidine and demonstrated the concomitant occurrence of a hypoprothrombinemia in both cases. The hypoprothrombinemia in each instance was readily remedied by synthetic vitamin K preparations administered intravenously. A similar occurrence was noted on the surgical service of Montefiore Hospital in a patient prepared for an intraperitoneal colostomy closure with sulfasuxidine. On the third postoperative day this patient had a massive hemorrhage into the bowel which coincided with a markedly increased prothrombin time. Pollard,<sup>8</sup> however, while treating four cases of chronic ulcerative colitis with 12 Gm. of sulfasuxidine daily for three weeks, failed to find any significant evidence of disturbance in the prothrombin time. Black and his group<sup>2</sup> administered sulfaguanidine to rats and demonstrated a significant increase in the prothrombin time as determined on a 12.5 per cent dilution of the rats' plasma.

The purpose of the present communication is to demonstrate the appearance of hypoprothrombinemia, as manifested by an increase in prothrombin time, when streptomycin is administered orally to reduce the colonic bacterial count.

### METHODS

The prothrombin time was determined by the method described by Shapiro<sup>14, 15</sup> which was based on the technics of Link and his co-workers.<sup>2</sup> Determinations were done on whole and 12.5 per cent diluted plasma specimens as suggested by these investigators.

Bacterial counts were obtained from stool specimens employing nutrient glucose beef infusion agar plates with serial dilutions of wet triturated stool;

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the results were read as viable bacteria per gram of wet stool. The preparation of the stool for culture followed the method proposed by Poth.<sup>9</sup> The bacterial counts from normal stools as obtained in the present study were strikingly lower than those reported in the papers reviewed.<sup>9, 10</sup> Nevertheless, the decrease in the bacterial counts that was noted after ingestion of the drug served the purpose of the study.

Four normal subjects were employed. The prothrombin times and the bacterial count in the stool were determined for each subject on two different days prior to the institution of oral streptomycin. Each subject was thereupon given one Gm. of streptomycin in a glass of tap water three times daily, and this regimen was continued for 14 days. The prothrombin time and the stool bacterial count were determined 24 hours after the inception of streptomycin by mouth and then at 48- to 72-hour intervals thereafter for 14 days.

No attempt was made to modify the diet of these subjects either as to type of food or its quantity. Two subjects received the regular hospital ward diet; the others continued their usual extra-hospital diets. It was suggested that each dose of the drug be taken by the subject one hour prior to each meal; this routine was adhered to in varying degrees by each of the four people studied.

#### DISCUSSION

The oral administration of streptomycin produced a diminution in stool bacterial count varying in the four cases from a 100 per cent reduction in one instance (Subject I) wherein culture of the stool revealed no growth to an 80 per cent reduction in Subject III who proved to be the most refractory. It is evident that the antibiotic varies in its effectiveness in different individuals as it does in its bacteriostatic action on different pathogens. In all subjects the maximum reduction in stool bacterial count was achieved within 48 hours of the institution of the streptomycin. Concomitant with the decreased bacterial counts in the stool, there appeared a significant elevation in the prothrombin times of both whole and diluted plasma specimens. The peak of the hypoprothrombinemia as measured by the maximum whole plasma prothrombin times was reached within one to four days; the maximum dilute plasma prothrombin times were reached within two to seven days. The increment in prothrombin time in dilute plasma was greater than that noted in the whole plasma specimens. This observation appears to be in agreement with the finding of Black *et al*<sup>2</sup> who suggested the use of dilute plasma prothrombin time determinations as a more sensitive means of detecting reductions in prothrombin levels in the blood.

In all subjects, there appeared to be an escape from the effect of the streptomycin; the bacterial counts began rising more or less progressively in every case within four to seven days after the drug was started. In three subjects, *E. coli* alone appeared in increasing numbers; in Subject III streptococci appeared first in great numbers and were then overgrown by streptomycin resistant *coli bacilli*. Roughly paralleling this increasing bacterial count was the rising level of prothrombin as evidenced by decreasing prothrombin times so that by the end of two weeks both dilute and whole plasma prothrom-

bin times approached pre-streptomycin values. This escape phenomenon is probably explained by the development of drug fastness. Several investigators have noted that bacteria rapidly acquire resistance to doses of streptomycin which were initially bacteriocidal.<sup>7, 12</sup> In the present study the development of bacterial resistance despite seemingly lethal concentrations of the antibiotic in the bowel lumen was possibly due to the presence of relatively inaccessible foci, such as the mucosal crypts of the colon. The appearance of drug fastness was irreversible; in all instances the bacterial counts remained high in the second week of treatment with streptomycin. The persistence of resistant bacterial strains in these individuals is of clinical importance. Resistant strains were found in patients treated for chronic urinary tract infections several months after the cessation of streptomycin therapy and in one instance Murray and his group demonstrated resistant bacteria some 11 months later.<sup>7</sup>

In addition to the development of drug fastness, the problem of uniform admixture of the drug with the bacterial substrate should be considered. Small quantities of the antibiotic at frequent intervals are probably more effective than more massive doses at longer intervals. Similarly, decreasing the fecal bulk by feeding a low residue diet should enhance the effectiveness of the streptomycin by allowing more immediate and prolonged contact between the intestinal bacteria and the drug.

It appears that the plasma prothrombin times are roughly inverse functions of the stool bacterial count. Almquist<sup>1</sup> has shown that numerous organisms such as *B. proteus*, *E. coli*, *streptococcus lacticus*, and *B. aerogenes* synthesize vitamin K when cultured on a vitamin K-free nutrient medium. The vitamin K manufactured by the coliform bacteria in the animal intestine, and readily absorbed in the presence of bile, probably accounts for the infrequency with which simple nutritional deficiency of vitamin K occurs in man.<sup>6</sup> It is possible that the hemorrhagic disease of the newborn which has been directly attributed to a demonstrable hypoprothrombinemia, occurs prior to the advent of a colonic flora in the newborn infant's sterile large intestine and, therefore, before the establishment of the endogenous source of vitamin K in the body. In the four subjects studied, once the remaining bacteria became drug fast and reproduced their kind, the synthesis of vitamin K approached a normal level of activity and the secondary hypoprothrombinemia disappeared.

In this study, no systemic toxic effects, other than the hypoprothrombinemia, were noted; this would seem to bear out the work of previous investigators<sup>7, 10, 12, 16</sup> who have demonstrated minimal absorption, if any at all, of streptomycin from the intestinal tract, with recovery of 90 per cent of the drug dose (given orally) in the stool.

Two subjects spontaneously remarked on the appearance of a sweet taste in the mouth after one day on streptomycin; the abolition of oral fetor was noted objectively in these two subjects. All four of the subjects noted a diminution in the gross bulk of the stool with a decided decrease in the fecal odor.

Oral streptomycin has been employed clinically in eight cases on the surgical service in the past six months in this hospital. All eight patients had

TABLE I: *Results*

## SUBJECT I

Date	Stool Bacterial Count (Colonies per Gm. of Wet Stool)	Prothrombin Time (Seconds)	
		Whole Plasma	12.5 % Plasma
2 days pre-streptomycin	53,000 <i>E. coli</i>	17.0	34.0
1 day pre-streptomycin	49,000	17.6	38.0
1 day post-streptomycin	no growth	23.8	51.0
2 days	100	22.5	58.0
4 days	200	21.6	75.4
7 days	2,200	21.4	74.5
9 days	6,300	20.6	66.0
11 days	2,000	20.4	62.8
14 days	16,400	18.0	38.5

## SUBJECT II

Date	Stool Bacterial Count (Colonies per Gm. of Wet Stool)	Prothrombin Time (Seconds)	
		Whole Plasma	12.5 % Plasma
2 days pre-streptomycin	11,000 <i>E. coli</i>	18.7	49.6
1 day pre-streptomycin	29,000	19.0	51.0
1 day post-streptomycin	200	22.3	61.3
2 days	200	22.1	56.3
4 days	1,000	22.6	60.4
7 days	2,000	22.4	72.2
9 days	4,000	17.9	60.5
11 days	8,600	18.2	49.8
14 days	3,400	18.0	51.3

## SUBJECT III

Date	Stool Bacterial Count (Colonies per Gm. of Wet Stool)	Prothrombin Time (Seconds)	
		Whole Plasma	12.5 % Plasma
2 days pre-streptomycin	32,000 <i>E. coli</i> predom.	19.8	50.8
1 day pre-streptomycin	38,000	18.6	50.4
1 day post-streptomycin	6,000	20.3	50.6
2 days	1,000	23.0	64.6
4 days	10,800 Streptococci predom.	19.9	54.0
7 days	57,000 Streptococci predom.	18.6	52.8
9 days	1,000 <i>E. coli</i> predom.	17.9	50.1
11 days	4,700	18.2	52.8
14 days	22,000	18.8	51.2

## SUBJECT IV

Date	Stool Bacterial Count (Colonies per Gm. of Wet Stool)	Prothrombin Time (Seconds)	
		Whole Plasma	12.5 % Plasma
2 days pre-streptomycin	53,000 <i>E. coli</i>	16.4	32.6
1 day pre-streptomycin	69,000	16.1	36.0
1 day post-streptomycin	300	20.8	48.6
2 days	100	22.0	51.1
4 days	3,000	21.4	49.8
7 days	10,000	18.7	40.7
9 days	21,400	17.2	36.0
11 days	9,600	19.0	40.4
14 days	18,400	17.0	38.6

proven or suspected lesions in the colon and received the drug in the course of preoperative preparation. In these operative cases, streptomycin has been administered in 0.5 Gm. doses every four hours for two days immediately preoperatively in conjunction with parenteral synthetic vitamin K. The adjuvant preparatory measures of low residue diet and mechanical cleansing by enemata have been continued as well. Where peritoneal contamination has been anticipated streptomycin has been given parenterally for two days preoperatively and two days postoperatively. The vitamin K preparations have been continued postoperatively for one week. All eight operative cases have had uneventful postoperative courses with maintenance of prothrombin time at pre-streptomycin levels. There have been no hemorrhagic complications.

#### SUMMARY

Reductions in stool bacterial count ranging from 80 to 100 per cent were achieved in four normal subjects by the oral administration of streptomycin. The maximum reduction in the bacterial counts in all subjects was noted within 48 hours of the institution of the streptomycin. It must be pointed out that the initial bacterial counts obtained in this study were very much lower than those reported by other authors employing the same technic.

Simultaneous with the decrease in the bacterial counts was the appearance of a hypoprothrombinemia as manifested by significant increases in prothrombin times determined in both whole and 12.5 per cent diluted plasma.

#### CONCLUSIONS

Where streptomycin is employed preoperatively in the surgery of the large bowel, the operative procedure should not be delayed for more than 48-72 hours after the drug is started.

It is suggested that vitamin K preparations be given before and after operation to prevent the appearance of the hypoprothrombinemia noted when streptomycin is given orally.

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#### ERRATUM

In the September 1948 issue of the *ANNALS OF SURGERY*, in the paper "The Response to Vagotomy in Idiopathic Ulcerative Colitis and Regional Enteritis" by Dr. Clarence Dennis, we failed to place a credit line with the color plate which appeared facing page 486 of this issue. This notice is as follows:

"Publication of these colored photographs has been made possible through the generosity of Mr. H. W. Rutzen, to whom the authors wish to express their thanks."

#### ERRATUM

In the article by Dr. Gordon Murray in the October 1948 issue of the *ANNALS OF SURGERY*, Figure 7 on page 850, through a typographic error, was printed upside down. The legend as printed should thus be interpreted with the illustration in reverse position to that printed. The same applies to Figure 8 on page 851 where the illustration is also upside down. The legend must also be re-interpreted in this case

## CONTROL OF THE COMMON ILIAC ARTERY DURING SACRO-ILIAC DISARTICULATION (HEMIPELVECTOMY)\*

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PREVENTION OF HEMORRHAGE is of particular importance during the wide dissection necessary in sacro-iliac disarticulation. This has been emphasized by Girard,<sup>1</sup> Gordon-Taylor,<sup>2, 3</sup> Judin<sup>4</sup> and Pack,<sup>5</sup> and various methods of vascular control have been described. Ligation of the external iliac artery, necessary in the removal of the extremity, does not control the parietal branches of the hypogastric artery encountered in the division of the pubic and sacro-iliac synchondroses and the structures deep in the pelvis. Mombert's procedure of temporary occlusion of the abdominal aorta is dangerous and unnecessary. Preliminary ligation of the common iliac artery achieves the necessary vascular control and makes the operative procedure relatively bloodless. However, the occurrence of necrosis of the posterior flap of the amputation following ligation of the common iliac artery is frequent. Judin<sup>4</sup> states that Brzosovski reports five patients who developed posterior flap necrosis after common iliac artery ligation and that Krassintzev's patient developed a necrotic flap after a similar ligation. Pack<sup>5</sup> reports this complication and states that such ligation should not be done routinely but "may be rarely indicated in poor risk patients where excessive bleeding, shock and prolonged operation are to be avoided at all costs."

Temporary control of the common iliac artery during the operative procedure will achieve the benefits of ligation without any of its undesirable effects. Any suitable type of direct arterial tourniquette may be employed. We have used the form of arterial control described by Babcock.<sup>6</sup> In the early stage of the operation, after division of the insertion of the rectus abdominis muscle and the attachments of the inguinal ligament, the peritoneum is retracted medially and the external iliac, hypogastric and common iliac arteries identified and a controlling tape placed around the common iliac artery. The ends of the tape are passed through the lumen of a short segment of soft rubber tubing and are drawn tight, compressing the artery against the tube. The tape is held taut by clamping a hemostat across the tube. (Fig. 1.) Occlusion of the common iliac artery is maintained throughout the operative procedure. After the hindquarter is removed, the controlling tape is released, thus preserving the continuity of the common iliac artery and its blood supply through the hypogastric artery and its branches.

Sacro-iliac disarticulation performed on three patients, with primary malignant tumors involving the hemipelvis, is herein reported. The standard technic outlined by Pack<sup>5</sup> with the addition of common iliac artery control

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\* Submitted for publication, February 1948.

was followed in each patient. It was observed that bleeding was far less than in previous experiences with the operation where the common iliac artery was not occluded. The absence of hemorrhage resulted in a shorter, less troublesome procedure in which shock did not occur at any stage.

## CASE REPORTS

Case 1.—J. W., white, male, age 20, was admitted to the Veterans Hospital, Portland, Oregon on January 17, 1947, complaining of a painful mass in the left gluteal region, first noted in November, 1946. An unsuccessful attempt at local excision had

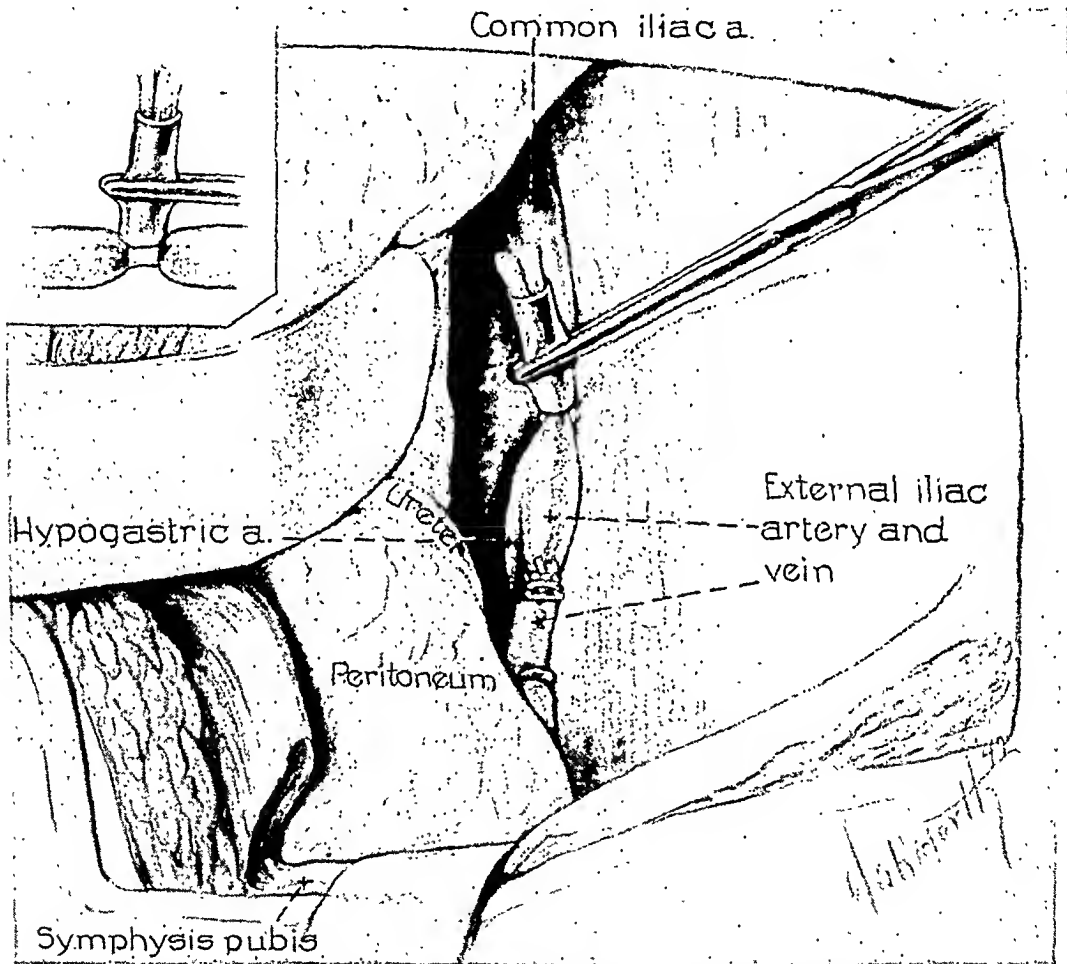


FIG. 1.—Drawing at operation illustrating method used for temporary control of the common iliac artery during sacro-iliac disarticulation.

been made at another hospital in December, 1946, after biopsy had shown the tumor to be an osteochondrosarcoma. Admission examination revealed a healed operative scar in the left buttock overlying a large, hard, tender mass. The left thigh was flexed and the patient could not bear weight on the extremity. Radiographic examination of the pelvis by Dr. Hyman revealed a dense bone condensation along the iliac margin of the left sacro-iliac joint, arising along the iliac crest. Near this plaque of bone sclerosis was a group of small, circular, translucent areas of bone destruction. The appearance was

## SACRO-ILIAC DISARTICULATION

that of a chondrosarcoma. Roentgenograms of the chest, long bones and skull were negative.

*Operation, March 10, 1947*—Under endotracheal, nitrous-oxide, oxygen, pentothal anesthesia, an incision was made beginning at the symphysis pubis, extending across the left iliac fossa to the anterior superior spine of the ilium, continuing downward over the greater trochanter and across the gluteal fold, then upward to the point of origin. The attachment of the left rectus abdominis muscle was cut and the inguinal ligament divided at its attachments to the pubis and the anterior iliac spine. The inferior epigastric vessels were ligated and divided and the spermatic cord retracted. The iliac fossa and the retroperitoneal pelvic space were exposed by retracting the detached abdominal wall and peritoneum medially. A large, hard, nodular tumor mass filled the iliac fossa, overlying and involving the sacro-iliac joint and extending into the pubis. It had spread posteriorly through the gluteal muscles into the superficial fascia and subcutaneous tissue. The common iliac, external iliac and hypogastric arteries were exposed. A controlling tape was placed around the common iliac artery which was occluded throughout the remainder of the operation. The external iliac artery was transfixed, doubly ligated and divided. The symphysis pubis was identified and divided with a chisel. It was observed that there was only slight bleeding during this procedure.

The patient was turned on his right side and the posterior dissection was carried through the muscles attached to the iliac crest and the gluteal attachments to the posterior surface of the sacrum. Returning to the anterior dissection the left sacro-iliac joint was exposed. The external iliac vein was now transfixed, doubly ligated and divided. The sacrum was divided medial to the sacroiliac joint. The gluteal and obturator vessels and nerves were sectioned. The sacrotuberous, sacrospinous and posterior sacro-iliac ligaments were divided. A normal pulsation in this artery, the hypogastric, and the stump of the external iliac artery was observed. The skin flaps were approximated, using through and through interrupted sutures of silk. During the operation the systolic blood pressure was never below 110.

*Pathology.* The ilium was the site of a large tumor mass involving a portion of the adjacent pubic bone and the sacro-iliac joint. The tumor was cartilaginous in consistency with central areas of cystic degeneration. Microscopic study revealed a typical osteo-

chondrosarcoma. The postoperative course was uneventful. Constant gastric suction through a Levine tube was maintained for four days. A Foley catheter was kept in the bladder until the third postoperative day. There was no abdominal distention or urinary retention following



FIG. 2.—Case 1.—Appearance of posterior skin flap, four weeks after operation.

removal of the tubes. The wound healed without infection and the posterior flap showed no necrosis. (Fig. 2.) Follow-up examination in February, 1948, one year after operation, revealed the patient to be alive but there were metastatic nodules in both lung fields.

## COMMENT

Because of the widespread nature of the tumor, sacro-iliac disarticulation was purely palliative in this case, but made it possible for a bedridden patient to be ambulatory for approximately one year. Control of the common iliac artery resulted in a minimum blood loss during the division of the pubic and sacro-iliac synchondroses and the deep pelvic dissection.

Case 2.—R. T., white, male, age 38, was first seen at the Veterans Hospital, Portland, Oregon on June 24, 1947, complaining of a painful mass in the left buttock of two years' duration. During the six months prior to admission, the mass had grown rapidly. Examination revealed a hard, immovable, firm ovoid mass in the left gluteal region. Radiographic studies of the pelvis showed areas of bone sclerosis and bone destruction

within the body of the left ilium, extending to the sacro-iliac joint, characteristic of a chondrosarcoma. A biopsy of the tumor, taken on June 26, 1947, showed it to be an osteochondrosarcoma.

*Operation, July 21, 1947.* A left sacro-iliac disarticulation was performed in the usual manner with temporary occlusion of the common iliac artery during the procedure.

Convalescence was uneventful save for a left lower lobe atelectasis which cleared after tracheal suction. There was a minimal amount of serious drainage from the wound, which was firmly healed in 21 days with no evidence of necrosis of the skin flap. (Fig. 3.)

*Pathology.* The specimen consisted of the left leg with the ilium, sacro-iliac joint, pubis and ischium. A firm, rounded tumor mass, 9 x 7 x 5 cm. arose from the external surface of the ilium, extending to the sacro-iliac joint. It appeared to be encapsulated, but greyish-brown strands extended from the tumor into the overlying muscles. A cross section of the tumor showed the presence of cystic spaces, partly filled with necrotic tissue. The area of the ilium from which the tumor rose showed patches of bone destruction and bone eburnation. On histologic examination, the tumor gave the characteristic picture of osteochondrosarcoma.

Follow-up examination, February, 1948, revealed a well-healed, painless stump.

Roentgenograms of the remaining bones of the pelvis and the lungs showed no evidence of metastasis.

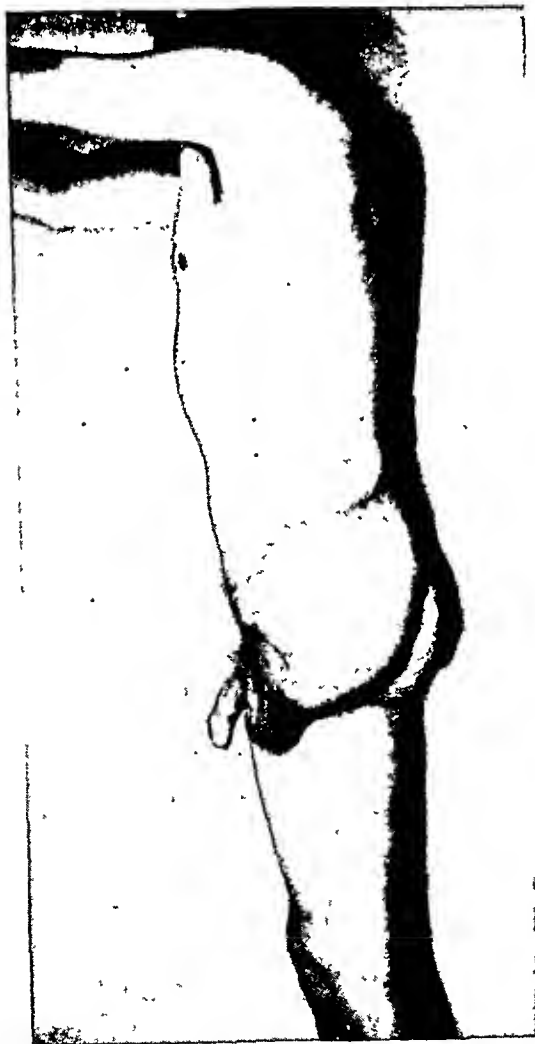


FIG. 3.—Case 2.—Postoperative photograph. Note primary healing.

COMMENT

Sacro-iliac disarticulation may result in prolonged arrest of the malignancy in this patient; because the tumor was well circumscribed, it had not involved the sacro-iliac joint and the dissection was wide of the involved ilium. Temporary occlusion of the common iliac artery provided excellent vascular control and the healing of the wound was by primary intention.

**Case 3.**—L. G., white, male, age 32, was admitted to the Veterans Hospital, Portland, Oregon on October 31, 1947, because of persistent pain in his left knee and thigh of four months' duration. One month before admission, the left thigh became swollen and a biopsy, taken by a private physician and studied at this hospital, revealed a periosteal type of sclerosing osteogenic sarcoma. Admission examination revealed a large tumor mass extending from the lower third of the thigh upward for a distance of 20 cm. Roentgenograms of the left femur showed broadening of the soft tissues around its lower half, within which there was a large bone tumor, characterized by extensive bony proliferation. There were many sclerotic and demineralized areas of bone within the shaft itself extending up to the greater trochanter. Radiographs of the lungs showed no metastasis.

**Operation, November 11, 1947.** A left, sacro-iliac disarticulation was performed and common iliac artery occlusion was maintained throughout the procedure.

Convalescence was uneventful save for considerable sero-sanguinous drainage from the wound. There was no necrosis of the flaps. (Fig. 4.)

Follow-up in February, 1948, showed a well-healed stump with no evidence of local recurrence or metastasis.

**Pathology.** The specimen consisted of an entire lower extremity which had been disarticulated at the pubic and sacro-iliac synchondroses. A large, irregular tumor, 20 x 15 x 10 cm. arose from the lower third of the femur and extended upward within and without the cortex to the greater trochanter. The tumor was composed of hard, cartilaginous grey-white material in which areas of hemorrhage and necrosis were present. It had invaded surrounding muscles from the knee to the greater trochanter. The microscopic diagnosis was osteogenic sarcoma.

COMMENT

Sacro-iliac disarticulation in this patient made possible the wide removal of a large osteogenic sarcoma of the femur which had extended to the greater trochanter both within and without the bone.



FIG. 4. — Case 3. — Postoperative photograph. Note viability of posterior skin flap.

## SUMMARY AND CONCLUSIONS

The value of temporary control of the common iliac artery is described in the report of three cases of sacro-iliac disarticulation. This addition to the standard technic of the operation makes possible a safer procedure with minimal blood loss. The danger of necrosis of the posterior skin flap incident to common iliac artery ligation is avoided.

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CORRECTION

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DR. I. S. RAVDIN *has requested that the ANNALS OF SURGERY publish the following correction:*

"My attention has been called to a statement which I made in "The Changing Scene in American Surgery," *ANNALS OF SURGERY*, 127: 666-675, 1948 to the effect that candidates for examination in plastic surgery must now be certified by the American Board of Surgery. This is an error."

I. S. RAVDIN.

# ADAMANTINOMA OF THE MAXILLA METASTATIC TO THE LUNG\*

## CASE REPORT

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The adamantinoma (ameloblastoma) is a rare tumor most commonly found in the jaw. It grows slowly, usually over a period of many years. This epithelial tumor arises either from the remnant of the enamel organ or from cell rests scattered along the length of the tooth. It is closely related to the dentigerous cyst and might well be called an enamel cell tumor. Enlargement of the bone, with rarefaction and thinning of the cortex, occurs as a direct result of the growth of the tumor, which may be primarily either solid or cystic, although degeneration of the solid type to form pseudo-cysts is common.<sup>1</sup>

The literature reveals that 80 to 85 per cent of adamantinomas arise in the mandible and about 15 per cent in the maxilla. Isolated case reports indicate other primary sites such as the tibia, the lip, the cheek, or even the pituitary body. The tumor has been generally considered to be benign, but metastases to other organs have been reported.

Chont<sup>2</sup> briefly reviewed the literature in October 1943 and reported one additional case of distant metastasis from an adamantinoma of the mandible. There have been reported 18 cases in which distant metastases to various sites have occurred; in nine of these the metastatic lesion involved the pulmonary parenchyma (Table I). Schweitzer and Barnfield,<sup>3</sup> reporting also in October 1943, describe a case wherein metastasis to the lung occurred from an adamantinoma of the mandible. These authors mention the fact that in only one previous instance, that case reported by Vorzimer and Perla, was there histologic proof of the ameloblastomatous nature of the metastatic lung tumor. It is reasonable to assume that the clinical impressions of the nature of the metastatic deposits in the pulmonary parenchyma were adequate to substantiate these diagnoses in spite of the lack of histologic proof. Indeed, in that case reported by Chont, the nature of the metastatic lesion was not verified histologically, but the clinical history leaves little doubt as to its true nature. However, the fact remains that of the nine reported cases of adamantinomas metastasizing to the lung, only two have been verified histologically. We are reporting a third.

## CASE REPORT

Mrs. M. C., a 56-year-old, white housewife, entered the University of California Hospital December 5, 1947. She was referred to us by her physician, Dr. Sidney Shipman. Sixteen months previously (September 1946) she had noted the onset of malaise and easy fatigability. Chest roentgenograms taken at that time demonstrated a soft shadow in the right lung field which was interpreted as bronchitis. The slight irritative

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TABLE I.—Summary of Reported Metastases from Adamantinoma

<i>Author of Case Report</i>	<i>Site of Primary Tumor</i>	<i>Duration of Primary Tumor</i>	<i>Sex</i>	<i>Age</i>	<i>Race</i>	<i>Sites of Metastases</i>	<i>Remarks</i>
	<i>Site of Primary Tumor</i>	<i>Duration of Primary Tumor</i>	<i>Sex</i>	<i>Age</i>	<i>Race</i>	<i>Sites of Metastases</i>	<i>Remarks</i>
1. EVE	Left Mandible	13 Weeks	F	60	W	Lumbar lymph nodes	
2. EWING	Unknown	Unknown	Unknown	Unknown		Cervical lymph nodes	
3. EWING	Unknown	Unknown	M	44	W	Lung	
4. GENTSCH	Left Maxilla	Unknown				Lymph nodes, sphenoid sinus, and malar bone	
5. HAVENS	Unknown	Unknown	Unknown			Unknown	
6. HAVENS	Right Mandible	Unknown	F	49	W	Right submaxillary region	
7. HEATH	Both Mandibles	28 Years	M	67	W	Local recurrence, metastases to thyroid fossa and pelvis	
8. HORSLEY	Right Mandible	20 Years	M	39	W	Local recurrence, metastases to cervical lymph nodes and lung	
9. NEW	Mandible	Unknown				Submaxillary gland	No recurrence after excision of primary tumor & involved submaxillary gland
10. SIMMONS	Left Mandible	15 Years	F	37	W	Recurred locally, 4 times; metastasized to cervical lymph nodes.	
11. SIMMONS	Right Mandible	15 Years	M	37	W	Local recurrence, metastases to cervical, submaxillary lymph nodes & lungs	
12. SPRING	Right Mandible	Unknown	M	5	W	Recurred 7 times, metastases to cranial bones, subcutaneous tissue of forehead	Metastases disappeared with X-radiation
13. VORZIMMER AND PERLA	Right Maxilla	31 Years	M	38	W	Recurred 5 times, invasion of antrum & nasal septum & metastases to lung	Metastases to lung histologically proved.
14. WEISSENFELS	Left Mandible	14 Years	M	26	W	Recurred, metastases to cervical lymph nodes, skin, submaxillary lymph nodes, & lung	
15. CHONT	Left Mandible	8 Years	F	55	W	Local recurrence, metastases to lungs	
16. OKINOUE	Mandible	Unknown	M	15	W	Metastases to lungs	Punch biopsy of lung. Tumor not adequate for diagnosis. No autopsy.
17. PHELPS	Maxilla	Unknown	M	42	W	Metastases to liver, ribs; tumor found within pulmonary vessels	Original lesion: ameloblastoma. Metastatic lesion: resembled carcinoma.
18. SCHWEITZER AND BARNFIELD	Mandible	Unknown	F	23	C	Recurred locally despite 24 operations; involved the maxilla & calvarium & metastasized to lungs	Histologically proved.
19. GRIMES AND STEPHENS	Left Maxilla	3 Months (Approximate)	F	46	W	No local recurrence, metastasis to lung	Histologically proved.

## ADAMANTINOMA OF THE MAXILLA

cough, without production of sputum or blood, persisted without change until her entry into this hospital. On only one occasion, while walking hurriedly, did the patient note right anterior chest pain. She received symptomatic medical therapy. There was no weight loss. Repeat roentgenograms in July 1947 and in September 1947 each showed an increase in the size of the lesion over that of previous roentgen examinations. Because of ankylosis of the temporomandibular joints, two attempts to perform bronchoscopy were unsuccessful.

In November 1937, ten years previously, an adamantinoma of the left maxilla was removed surgically. The operative procedure was preceded by an extraction of the left upper third molar tooth resulting in a chronically draining area which was finally removed with the subjacent tumor mass. She received postoperative radium therapy which resulted eventually in a partial ankylosis of the temporomandibular joints, some of which she had overcome.

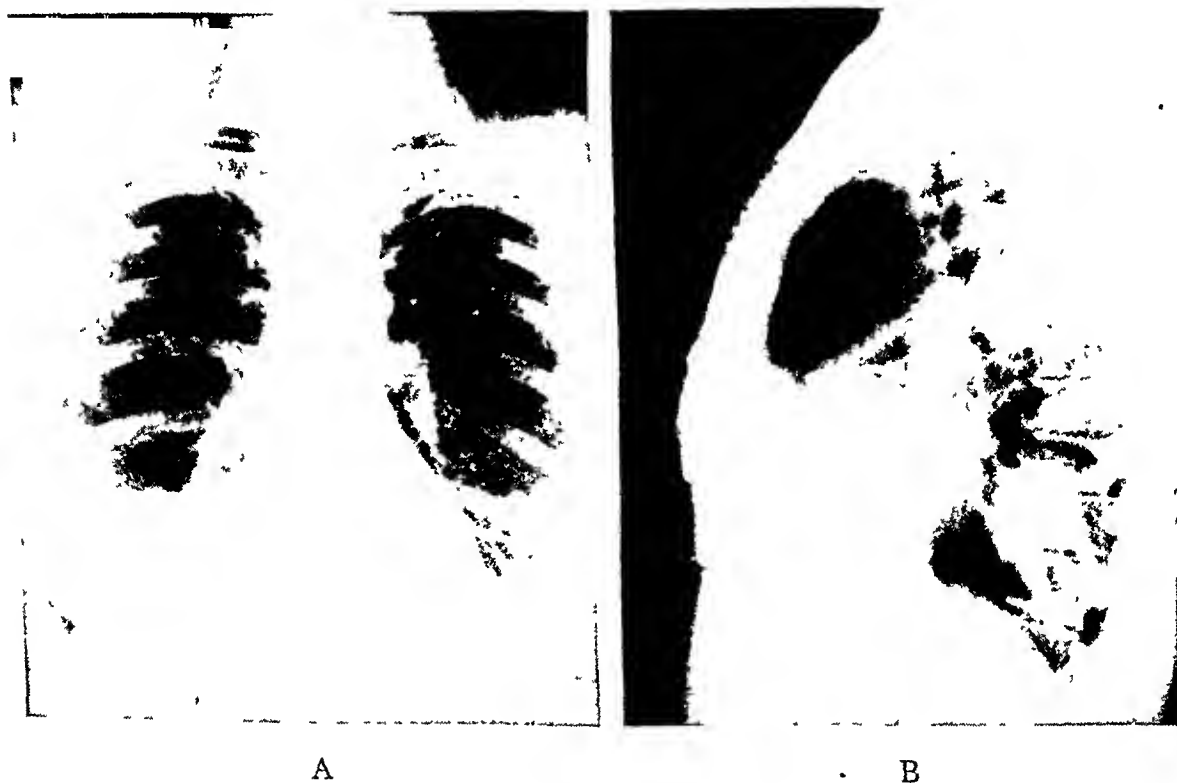


FIG. 1.—Roentgenograms taken in November 1947 illustrating the increase in size of the right lower lobe lesion over that of July 1947. The circumscribed nature of the mass is maintained. It is more apparent on the lateral view than in the previous films.

Major system inventory was non-contributory in respect to the pulmonary lesion. Progressive bilateral eighth nerve deafness had been present since the age of 18, requiring the constant use of a mechanical hearing aid.

Physical examination revealed a well nourished white female, not acutely ill, with normal temperature, pulse and respiration. The blood pressure was 126/72. The left upper alveolar ridge and the adjacent maxilla, as well as the floor of the left antrum of Highmore, had been surgically removed. The posterior aspect of the left half of the hard palate also had been removed, allowing one to view a rather large cavity in the roof of the mouth extending posteriorly along the base of the skull for a distance of approximately 6 to 7 cm. A well-fitting dental prosthesis effectively closed off these openings. The mucosa surrounding the previously involved area, although exhibiting considerable scarring, was completely smooth and without evidence of recurrence of the original tumor. There were no palpable lymph glands or other masses in the cervical region.

Expansion of the chest was equal bilaterally. There was an area of decreased breath

sounds, overlaid with an exactly similar area of dullness, in the right lower lung field posteriorly. There was no evidence of an intrapleural collection of fluid.

Examination of the abdomen, pelvis and rectum revealed only normal findings throughout. Urinalysis showed normal constituents, and the hematologic study showed no anemia.

Roentgenograms of the chest (November 1947) showed a circumscribed density of the lower lobe of the right lung occupying its posterior basal division. Comparison with the films taken three and five months previously (July and September 1947) showed that the lesion had again definitely increased in size. (See Figure 1.)



FIG. 2.—Photograph demonstrating the cut section of the tumor. The lower lobe bronchus (top left), though immediately adjacent to the mass in one area, is not involved by it. The surrounding pulmonary parenchyma is only slightly compressed and is not otherwise abnormal.

It was our opinion that we were dealing with (1) a slowly growing, low-grade primary malignancy of the right lower lobe, (2) a metastatic tumor from a primary lesion in one of the major systems not demonstrable by the usual clinical methods, or (3) a metastatic tumor from the original focus in the left maxilla.

Thoracotomy was carried out December 6, 1947. The hard, circumscribed rounded mass lay deep in the parenchyma of the right lower lobe and was entirely confined within it. The hilar and mediastinal lymph nodes in the area of dissection were soft,

# ADAMANTINOMA OF THE MAXILLA

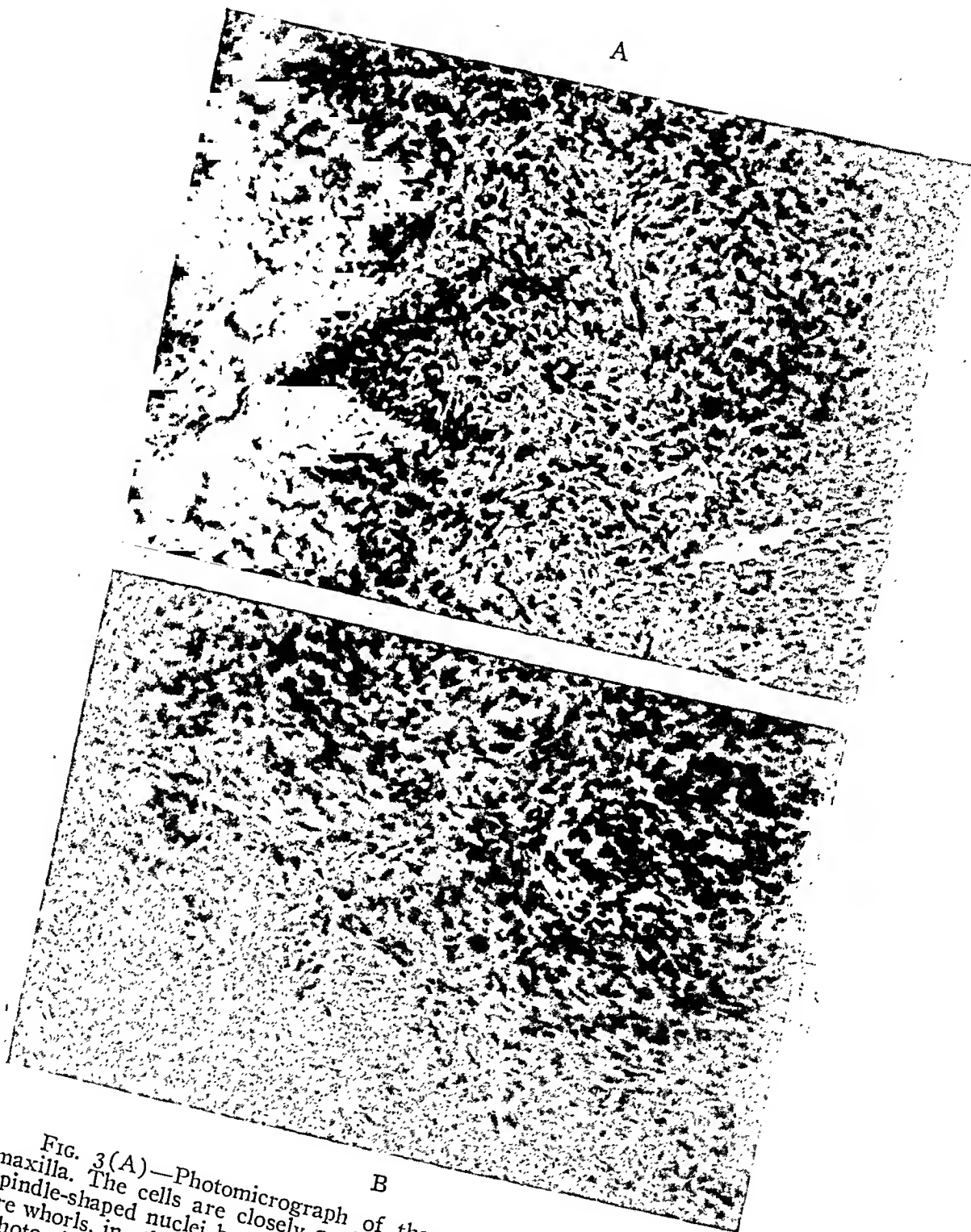


FIG. 3(A)—Photomicrograph of the original lesion of the left maxilla. The cells are closely packed together and exhibit ovoid or spindle-shaped nuclei but only scanty cytoplasm. In some areas there are whorls, in others suggestive glandular arrangements. FIG. 3(B)—Photomicrograph of the metastatic tumor of the lung. Note the dense cellular pattern corresponding to that of the original lesion. The similarity between the two lesions is marked. There is apparently no correlation between the histologic pattern of the adamantinoma and its ability to metastasize.

pigmented, and were not grossly involved by abnormal tissue. There were no notable adhesions. The nature and characteristics of the tumor made one think of a secondary metastatic deposit. A right lower lobectomy was therefore accomplished. The post-operative course was entirely uneventful and the patient was discharged to her home on the 11th postoperative day.

The excised lobe of the lung contained in its center a firm, round, well circumscribed mass 3.5 cm. in diameter which was homogeneous and pinkish-white on cut section. The surrounding lung tissue showed little evidence of compression, and in general was quite well aerated. No communication between the mass and a bronchus could be demonstrated. (See Fig. 2.)

Microscopically, the tumor was composed of closely packed masses of large cells with ovoid or spindle-shaped nuclei and scanty eosinophilic cytoplasm. The cells resembled basal cells, and in some areas were palisaded at the margin. There was invasion of the surrounding connective tissue by the malignant cells. In some areas the cells were arranged in whorl-like patterns suggestive of rosettes. There was a tendency toward glandular pattern in a few areas, and occasionally the cells resembled columnar epithelial cells. In most areas, however, the masses of tumor cells were separated from the pulmonary alveoli by a heavy layer of connective tissue. Microscopic diagnosis: Adamantinocarcinoma. (See Figs. 3A and 3B.)

#### DISCUSSION

There is general agreement that local recurrence of an adamantinoma frequently occurs, though distant metastases are rare. Of the approximately 500 adamantinomas reported in the literature, those 18 which metastasized regionally or distally represent 3.6 per cent, while those metastasizing to the lung represent 1.8 per cent of the total.

Ewing<sup>4</sup> considered all adamantinomas to be malignant because of their tendency to recur and to invade bony structures in the immediate neighborhood. Many writers on the subject agree that local recurrence is the rule rather than the exception. However, some explain the high rate of local recurrence by the fact that the tumor may infiltrate the bone more than is apparent to the naked eye so that incomplete removal may be followed not by actual recurrence due to inherent malignancy, but rather by persistence of the tumor.

Distant metastases, however, can be explained only by the malignant nature of the primary ameloblastoma. The three possible routes of transfer to the lung are (1) by inhalation through the tracheo-bronchial tree during the course of an operative procedure, (2) via the lymphatic chains, and (3) by blood transport. It is reasonable to assume that in the case being reported the tumor tissue reached the lung by way of the blood stream, since involvement of lymph nodes in the neck or mediastinum was not observed, nor was there an intimate association of the tumor with a bronchus.

The fact that metastatic adamantinomas are likewise slow growing is well borne out in this case. It is probable that the metastasis occurred before or during the period of treatment of the original tumor in 1937, since no evidence of tumor tissue has subsequently been noted in the region of the left maxilla.

#### SUMMARY AND CONCLUSION

A case history is presented in which an adamantinoma of the left maxilla metastasized to the right lung. Histologic verification of the nature of the

primary and secondary lesions is presented. This is the third reported case of metastatic adamantinoma of the lung substantiated by microscopic examination. Although the adamantinoma is characterized mostly by local recurrence, in a small percentage of cases there are distant metastases.

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#### ANNOUNCEMENT OF VAN METER PRIZE AWARD

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Madison, Wisconsin, May 26th, 27th and 28th, 1949, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed 3000 words in length; must be presented in English; and a typewritten double spaced copy sent to the Corresponding Secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia, not later than March 15th, 1949. The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author if it is possible for him to attend. The essay will be published in the annual Proceedings of the Association. This will not prevent its further publication, however, in any Journal selected by the author.

# SEVERE CRUSHING INJURY TO THE CHEST\*

REPORT OF A CASE HAVING EXTENSIVE BILATERAL RIB FRACTURES  
SUCCESSFULLY TREATED BY PERICOSTAL SKELETAL TRACTION

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THE AUTOMOBILE HAS MADE crushed chest a comparatively common and not infrequently fatal accident. Cardio-respiratory embarrassment due to the development of hemothorax and pneumothorax may be an outstanding feature in these injuries. More commonly, however, symptoms of this type are delayed 48 to 72 hours and are produced by a clinical triad: intrabronchial hemorrhage, ineffectual cough, and a type of anoxia which has been described in another communication.<sup>1</sup> An exceptionally severe injury producing multiple bilateral rib fractures may be followed immediately by grave cardio-respiratory embarrassment due to violent paradoxical movement of the chest wall. The latter disability may be of such magnitude as to require prompt correction as a life saving measure. The case report which follows is presented as an example of this type. The injuries sustained by this patient include:

- (1) Bilateral anterior fractures of ribs 1-7 inclusive.
- (2) Fractured skull.
- (3) Compound fracture of the right radius and ulna.
- (4) Compound fracture of the right tibia and fibula.
- (5) Kidney injury productive of hematuria for 48 hours.

Complications developing during the course of treatment include:

- (1) Left hemiplegia.
- (2) Hemopneumothorax.
- (3) Massive subcutaneous emphysema.
- (4) Acute dilatation of the stomach.
- (5) Fecal impaction.

## REPORT OF CASE

M. G., a white male shoemaker, age 51, was injured in an automobile accident on November 21, 1946, when he drove his car into a tree. His companion riding in the front seat was killed instantly and the patient was thrown against the steering wheel. On admission to the hospital one hour later he was unconscious, cyanotic and pulseless. Compound fractures of the right forearm and the right leg were present. Extensive bilateral rib fractures (Fig. 1) could be diagnosed by inspection, and paradoxical movement of the sternum and anterior chest wall was of extraordinary violence. The sternum appeared to be depressed almost to the bodies of the dorsal vertebrae with each inspiratory effect.

The fractured arm and leg were splinted; oxygen was administered by B. L. B. mask; an infusion of plasma was started; and the patient was taken to the operating room. Bronchoscopy without anesthesia was done, and a small amount of bloody secretion

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\* Submitted for publication, April 1948.

## CRUSHED CHEST INJURY

was aspirated. This was not followed by any improvement in his condition. The anterior chest wall was then quickly prepared for operation, and proceeding again without anesthesia, an incision about 3 inches long was made over the left third rib near its cartilaginous junction where the paradoxical movement was most violent. When the rib was exposed it was grasped with a large towel clip just medial to the fracture site. Strong traction on this instrument reduced by approximately 50 per cent the paradoxical movement which now became most severe at a lower level on the same side. A second incision was then made over the left fifth rib and it was grasped medial to the fracture

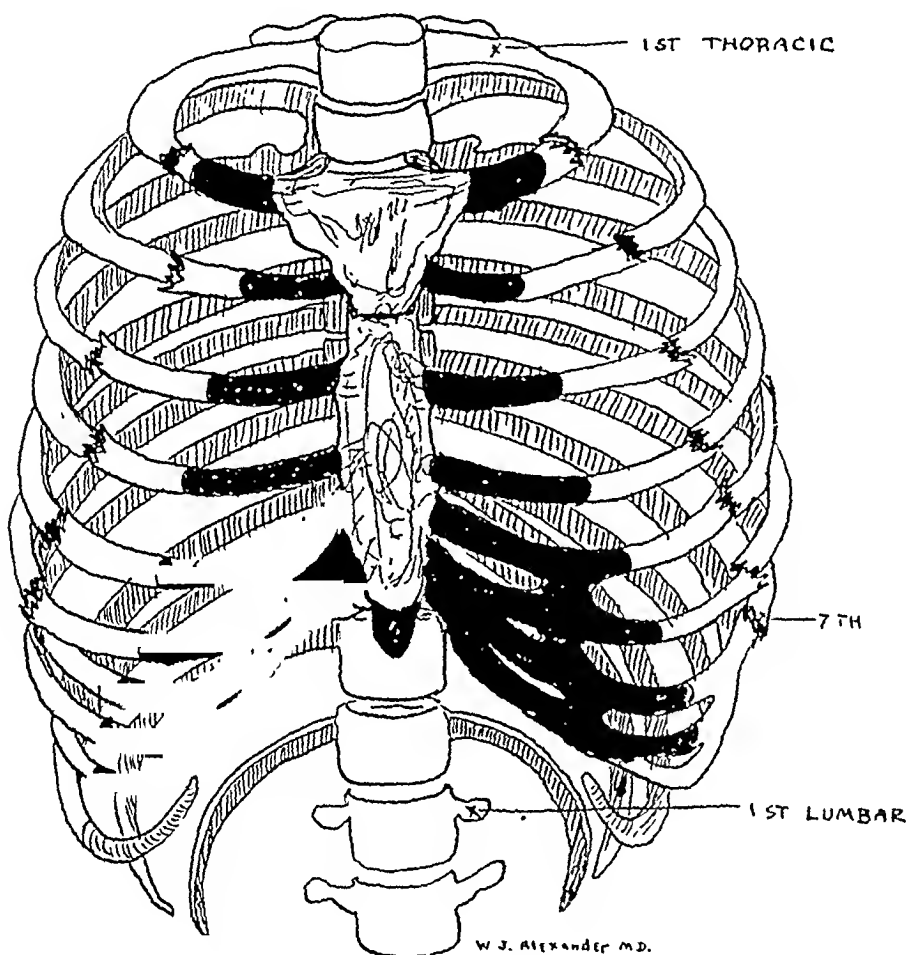


FIG. 1.—An accurate drawing which illustrates the fractures.

site with another towel clip. Strong traction on both instruments now resulted in reduction of the paradoxical movement by approximately 75 per cent and appeared to lock the fragments of the fractured ribs on the right side. The patient's breathing immediately became less labored and his color improved.

The wounds were closed and the patient was then transferred to a fracture bed. Traction was maintained by suspension to an overhead frame using rubber tubing and wire, as illustrated in Figure 2. The foot of the bed was elevated about 18 inches. Maximum stability of the chest was obtained by changing slightly the direction and the amount of traction. A transfusion of citrated blood was started and oxygen was administered by both nasal catheter and B. L. B. mask. During the first 24 hours 1,000 cc. of plasma and 1,000 cc. of blood were given. He required catheterization and the urine was bloody.

Shock was rapidly corrected but the patient remained unconscious. Accumulation of bloody tracheobronchial secretions productive of increased respiratory embarrassment followed within the first six hours after his injury. This was relieved by tracheal



aspiration using a 16 F. catheter. Clearing the tracheobronchial tree by this method was required thereafter at two to six hour intervals for the entire period of 24 days during which the traction was maintained.

The morning following injury the patient was semiconscious; his color was improved but some subcutaneous emphysema had developed. The urine was bloody. Frequent tracheal aspirations were done during the day and a large amount of bloody mucus was

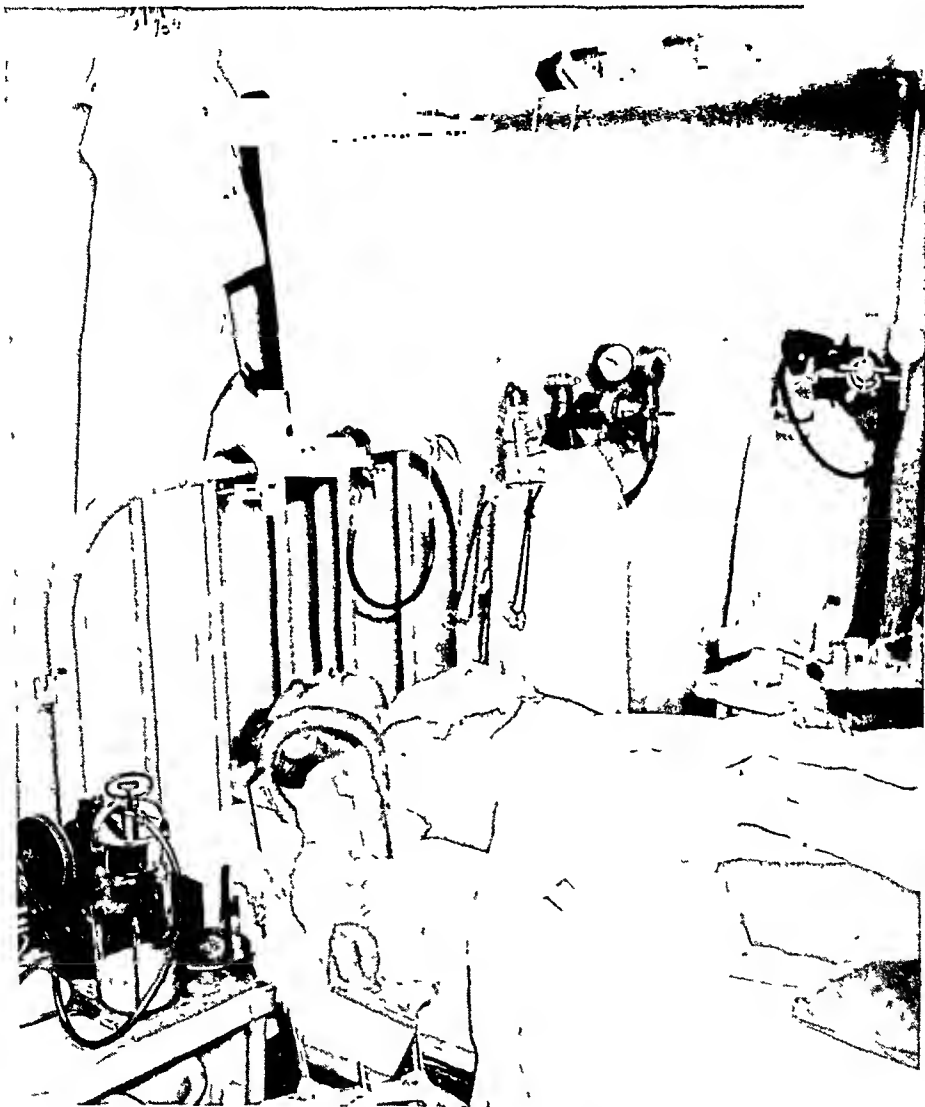


FIG. 2.—Photograph illustrating the application of traction, which was estimated at ten pounds. Note the suction machine which was kept constantly at the bedside.

aspirated. In spite of this measure and the administration of oxygen by both B. L. B. mask and nasal catheter, dyspnea and cyanosis increased alarmingly. A bedside roentgenogram demonstrated an enormous dilatation of the stomach. A Levine tube was passed which resulted in a prolonged audible escape of air. At the same time the upper abdominal wall flattened; this was followed by remarkable improvement.

The subcutaneous emphysema steadily increased in amount and on the third day of his admission it had progressed to a degree sufficient to give the skin of the anterior chest

## CRUSHED CHEST INJURY

wall a tenseness similar to that of an under-inflated football. The patient was now again alarmingly dyspneic and cyanotic. About 3,000 cc. of this air were removed, using a large needle and a pneumothorax apparatus. Deflation of the emphysema was followed by immediate relief of symptoms, but the air continued to accumulate, doubtless due to the presence of a bronchial fistula. An incision in the axillary area 2 inches long was then made into this air-containing space. This permitted continuous escape of air for the next 24 hours, after which no further leakage or accumulation occurred.

Administration of penicillin, 25,000 units every three hours, was begun at the onset. After the third day, 50,000 units were instilled twice daily through the intratracheal catheter after completion of aspiration. The bronchial secretions which were first bloody and later purulent, decreased in amount and became mucoid in character after the first week.

Seven days after admission a definite left hemiplegia had developed. He was fairly alert, nevertheless, and at this time he was able to take a liquid diet. A neurosurgeon was asked to examine the patient and on December 11th (19th day of admission) an exploratory burr hole over the right motor area was made\* and an intracerebral hematoma was found and aspirated. This operation was performed without moving the patient from his bed. The procedure was well tolerated and no immediate change in his condition followed. Within three days, however, considerable improvement in his sensorium occurred and steady improvement followed thereafter. A low grade septic type of fever, present from the first, continued for 17 days although the compounded fractures remained free of infection.

Increased stability of the chest permitted some decrease in the amount of traction after the second week and oxygen therapy was discontinued. On numerous occasions during the first and second weeks, the traction was momentarily released. When this was done severe paradoxical movement and labored respiration followed immediately, and the patient became dusky and panicky after about 30 seconds. After three weeks the chest wall was only slightly mobile. After 24 days the traction was entirely released and the following day the towel clips were removed. The operative wounds healed without infection. At this time the patient developed nausea and severe abdominal cramps. Rectal examination showed the presence of a fecal impaction. This was removed with prompt relief of his abdominal symptoms.

Subsequently, open reductions of the fractured forearm (January 16, 1947) and right leg (February 4, 1947) were done.\*\* Beginning eight weeks after injury some movement of the left leg was possible and thereafter improvement of this extremity was rapid. Five months after injury slight movement of the left arm and hand was possible and considerable additional improvement in this extremity has since occurred. Bony union of the fractured right arm and right leg followed operation. At the time of the patient's discharge from the hospital (June 29, 1947) he had a hemiplegic gait, but with a little assistance was able to walk with a cane.

### DISCUSSION

In general, comparatively few patients with crushed chest injuries will require skeletal traction. The indication for this treatment arises in an occasional, exceptionally severe, injury of this type in which paradoxical movement of the chest wall is the outstanding clinical feature. The latter disability is prejudicial to normal intrathoracic pressures and thereby impairs both the function of ventilation of the lungs and the filling of the heart. The cardio-respiratory embarrassment which follows is directly proportional to the violence of the paradoxical movement.

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\* Operation by Dr. J. Worden Kane.

\*\* Operation by Dr. John T. Kane.

Before skeletal traction is applied it should be carefully determined in every instance that the paradoxical movement is not contributed to, or actually precipitated, by other complications. The writer has observed several instances of severe crushed chest injuries in which paradoxical movement of the chest wall was a delayed complication. All of these patients had either extensive single unilateral rib fractures, or unilateral double fractures of several adjacent ribs. In every instance the chest wall was stable at the onset. Paradoxical movement occurred several hours or several days after injury when dyspnea developed due to hemothorax, pneumothorax, or bronchial obstruction. In these patients, immediate and dramatic relief from both the dyspnea and paradoxical movement followed the aspiration of blood or deflation of air from the pleural space or the clearing of blood and secretions from the tracheo-bronchial tree.

From the foregoing it is seen that skeletal traction is indicated in a small group of chest injuries in which the fractures of the thoracic cage alone are sufficient to produce paradoxical chest wall movement productive of grave cardio-respiratory embarrassment. For practical purposes it appears that few, if any, patients will require such treatment unless severe paradoxical movement is present immediately after the injury. It seems likely that traction will rarely be required in instances of single unilateral rib fractures. Such treatment may occasionally be necessary in those having unilateral double fractures of several adjacent ribs. As illustrated in this report, extensive bilateral rib fractures near the sternum which allow mobilization of a large portion of the chest wall may present an urgent indication for skeletal traction. Simplicity, and absolute reliability, are features which recommend the pericostal towel clip method with elastic overhead traction described in this case report.

A survey of the literature shows that the use of pericostal skeletal traction in crushed chest injuries has been proposed by Eloesser<sup>2</sup> and Wise.<sup>3</sup> In a personal communication, Eloesser reports the use of this type of traction in several cases but no published case report has been found in which this treatment was applied. In the comparatively few cases in which other forms of skeletal traction or fixation are reported, a delay of several hours or several days is noted between the time of injury and the time that such treatment was instituted. None of these had extensive bilateral anterior fractures near the sternum which permitted early violent paradoxical movement. This indicates that the chest injury sustained by the patient reported here may be one of unprecedented severity to have been followed by recovery.

Treatment of a fractured sternum with traction has been reported by Joslow<sup>4</sup> who used a coat hanger. McKim<sup>5</sup> reported a similar case which he immobilized with Kirschner wires. The Drinker Respirator was utilized successfully in a severe crushed chest injury with bilateral fractured ribs by Hazen.<sup>6</sup> Jones and Richardson<sup>7</sup> used skeletal traction applied to the sternum in a child having eight unilateral fractured ribs. The traction was applied with a "bullet forceps such as is used to grasp the cervix in gynecologic cases." The

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traction was maintained with "weights and pulleys attached to a rainbow frame." Traction was removed after 48 hours without change in the child's condition. Their patient recovered.

A crushed chest injury which allows paradoxical movement of sufficient severity to require skeletal traction will invariably be accompanied by other complications. In all injuries of this type, intrabronchial hemorrhage associated with ineffectual cough productive of anoxia, atelectasis, and pneumonia should be anticipated. In the case reported here, effectual cough was impossible during the period that traction was maintained. This necessitated the frequent use of tracheal aspiration by the method of Cameron Haight.<sup>8</sup> This invaluable procedure yielded 2-4 ounces of mucopurulent bronchial secretions daily. After instruction, this method of treatment was effectively applied by the patient's nurses. Tracheal aspiration, together with elevation of the foot of the bed, and liberal use of penicillin, is believed to have made possible the avoidance of any pulmonary complication. The alarming symptoms which followed monetary release of the traction appear to demonstrate conclusively that he could not have been successfully treated without this form of stabilization.

### SUMMARY

A crushed chest injury is reported in which violent paradoxical movement of the chest wall and severe cardio-respiratory embarrassment were the outstanding features. Treatment by a combination of skeletal traction, tracheal aspiration, and the administration of penicillin intramuscularly, and intratracheally, was followed by recovery.

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# HERNIATION OF THE HEART\*

## THROUGH A PERICARDIAL INCISION

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THE FOLLOWING CASE is of interest because of the infrequency of the complication, the seriousness of the symptoms subsequent to the cardiac herniation and the dramatic recovery following its reduction.

The sequence of events is as follows: Mr. P., a rather frail, 53-year-old male, in fair general condition, was operated upon by us for a carcinoma of the left lung. The operation was uncomplicated except that there was a dense, broad adhesion which firmly bound the lower part of the upper lobe of the left lung to the parietal pericardium at the level of the conus arteriosus of the heart. Because of the density of the adhesion and its proximity to the tumor in the lung, we thought that the carcinoma might have infiltrated into it and for this reason decided to remove the pericardium with the affixed lung rather than cut through the adhesion. This resulted in a defect of the anterior pericardium about  $2\frac{1}{2}$  inches in diameter through which the conus and the base of the pulmonary artery could easily be seen.

Before closing the chest wall at the end of the operation, the advisability of suturing the pericardium was discussed, but we decided against it because closing this large defect would have constricted the outflow tract of the heart. I must admit that the possibility of a herniation at this site never occurred to us.

The pneumonectomy had been performed through a posteriolateral incision with the patient lying on his right side. At the end of the operation, the patient's condition was good, he was pink, his pulse was 90, his blood pressure was 110/90. Careful aspiration of the trachea and bronchus had been carried out during operation both by the anesthetist and once by us just before closing the bronchial stump, so that his respirations were free and easy.

After the dressings had been applied he was rolled over on his back, lifted on to the cart and placed gently on his operated (left) side. A moment after this was done, the entire picture changed! The patient went into collapse. His radial pulse became imperceptible, his blood pressure could not be obtained, he was pale and started to perspire. Thinking the condition was due to a cardiac shift, he was immediately put flat on his back and oxygen was administered through the tracheal tube, which, fortunately, had not yet been removed. The picture did not change. The pulse still remained imperceptible and the condition was still one of profound shock. A bottle of blood, which was available, was hooked to the

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\* Submitted for publication June, 1948.

indwelling intravenous needle in the ankle and its contents forced into the vein. Even after the entire bottle had been injected, the patient's condition did not improve. It was noted that there was no difficulty in getting air into and out of his right lung, nor did hurried examination show any evidence of unusual mediastinal shift. Thinking that the condition was most probably due to a massive internal hemorrhage, and realizing that the patient would die if nothing were done, he was put back on the operating table, pushed back into the operating room, dressings removed and draped ready for reopening the chest wall. The diagnosis of hemorrhage was strengthened by the aspiration of a few centimeters of sanguinoseous fluid from the catheter drainage tube. (Note—We usually do not drain the chest cavity following pneumonectomy, but did in this case because there had been innumerable adhesions between the visceral and parietal pleura over the entire posterior lung field and we felt that there might be a great deal of pleural reaction with a large effusion.)

It must have been at least 25 minutes from the sudden onset of shock to the start of the second operation.

When the chest cavity was re-opened through the former incision, the picture that presented was startling. The apex of the heart almost protruded through the incision. The heart appeared to be standing on end and pointing directly upward, that is, perpendicular to its usual position. It was entirely devoid of pericardial covering; it was dilated; its veins were greatly engorged and it was beating very feebly but at an extremely rapid rate. The diagnosis was obvious, namely, the heart had herniated through the pericardial defect. The rim of the pericardial opening was easily located and slit and the heart slid back into its normal position. After a few more twitches, it started to regain its normal form of contraction, and within less than half a minute was beating strongly. The cardiac dilatation and the venous engorgement receded quickly. The anesthetist was able to pick up the pulse at the temple within a few seconds and the first blood pressure reading after the cardiac replacement was 90/50 and soon 110/70. Inspection now of the left pleural cavity revealed nothing abnormal, a small amount of serosanguineous fluid, no signs of severe hemorrhage and the great vessels well tied off and the stump of the bronchus well buried in the mediastinum. It seemed to us that the entire episode was due to the angulation and the strangulation of the outflow zone of the heart incidental to the herniation. In order to guard against a recurrence, the opening in the pericardium was enlarged by removing practically the entire anterior pericardium.

By this time, the general condition of the patient was excellent. The wound was resutured; the dressings reapplied. The patient was gently turned on his back and no change in condition noted. He was returned to his room and kept on his back, with the backrest slightly elevated for the rest of the day. Needless to say, he was carefully watched!

His convalescence from here on was uneventful. He seemed to show no signs of damage due to the period of profound shock. His mentality was

normal. There were no renal manifestations. The day after the operation, he was allowed to turn at will. He preferred lying on his back, but could turn on his right side. However, whenever he started to turn on his left side, for the first week or ten days, he felt "as if he were going to faint." This also happened whenever he raised himself suddenly. These symptoms were accompanied by the objective signs—pallor, increased pulse rate up to 120 and thready pulse, and a drop in his blood pressure to 90/60. Electrocardiographic study immediately after operation and during the convalescence was not particularly significant.

By the end of the third week after operation, he was well enough to leave the hospital; he could turn in any position he wanted to but still did not like to lie on his left side because it made him "feel funny."

Now six months after operation, he is doing well, he looks in as good health as before operation, he is out-of-doors, but does not yet feel able to go back to his job, which was one of physical labor.

#### SUMMARY

A patient was operated upon for a carcinoma of the left lung. The pneumonectomy included the removal of an adherent piece of parietal pericardium about  $2\frac{1}{2}$  inches in diameter overlying the region of the conus arteriosus. When the patient's position was shifted after the operation, the patient suddenly went into profound shock which he was able to tolerate for about 20 minutes, during which time means to combat the shock were tried. When the chest was re-opened, it was found that the heart had herniated through the pericardial defect and had become angulated and partially strangulated. As soon as the herniation was reduced, the symptoms disappeared. Recurrence was prevented by removing practically the entire anterior parietal pericardium. Recovery was complete and the removal of the pericardium seemed to produce no untoward effects.

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#### UROLOGY AWARD

*"Urology Award"*—The American Urological Association offers an annual award of \$1000.00 (first prize of \$500.00, second prize \$300.00 and third prize \$200.00) for essays on the result of some clinical or laboratory research in Urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals.

"The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Biltmore Hotel in Los Angeles, May 16-19, 1949."

For full particulars write the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis 3, Tennessee. Essays must be in his hands before February 15, 1949.

# MYCETOMA — MADURA FOOT\*

A CASE OF MYCETOMA PEDIS IN CHICAGO

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THE EARLIEST DESCRIPTION OF MYCETOMA was reported in the Madras Presidency of India in 1842 by Gill.<sup>1</sup> The condition had been known there for many years. In 1846 Colebrook from the same dispensary described further cases and introduced the term Madura foot for a distinct disease entity of that region. It was Vandyke Carter<sup>2</sup> who studied the condition over a period of years, 1860–1874, describing the changes caused in the bony structures and soft tissues of the affected parts and then identified filaments of a fungus found in the grains within the sinus tracts of the diseased area. He introduced the term Mycetoma, literally fungus tumor, for the condition, since he found it could affect other parts of the body than the foot. His pen and ink drawings and his descriptions indicate a true fungus with septate filaments and chlamydospores was studied. He classified his cases by the color of the grains found in the sinus tracts as pale or white, black and red.

Pinoy<sup>3</sup> in 1913 recognized the possibility of classifying cases of mycetoma by grouping the causative organisms, and in 1916 Chalmers and Archibald<sup>4</sup> reviewed the reported cases and published such a classification dividing them into two groups:

GROUP 1. Maduromycoses, caused by true fungi exhibiting septate filaments usually with chlamydospores, and

GROUP 2. Actinomycoses, due to delicate nonseptate filaments of the Actinomyces which belong to higher bacteria.

The basis for this classification has had to rest principally upon prepared sections from preserved material in the absence of cultures. After a critical examination of the first 25 cases of mycetoma recorded in Canada and the United States, Jones and Alden<sup>5</sup> in 1931 reported that 16 could not be definitely classified because of inadequate data. Seven cases were clearly of Maduromycoses and two were of Actinomycoses. In 1945, Burns, Moss and Brueck<sup>6</sup> published a chart covering the 38 cases reported up to April 1944. The chart which follows gives a similar picture of each case reported in this country from that date to and including the present case, thus bringing all recorded cases up to the present time.

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\* Submitted for publication, January 1948.



TABLE I.

Number of Case	Authors	Date Reported	Age at Infection	Sex	Race	Occupation	Site of Infection	Where Acquired	Predisposing Trauma	Color of Grains	Classification of Organism	Cultures
1.	Symmers and Sporer <sup>12</sup>	May 1944	67	M	American (New York)	Clerk	Hand	New York	Splinters in hand (fall)	Black	Maduromycoses Chlamydospores	Negative <sup>19</sup>
2.	Venable and Gaston <sup>13</sup>	June 1944	8	M	Negro	Farmer's child	Left foot	Georgia	Glass in foot (barefooted)	Yellow	Maduromycoses	Cultured and studies
3.	Gottlieb, A. <sup>14</sup>	June 1944	42	M	Mexican	Farmer	Left foot	California	Callus near heel	Black	Maduromycoses Clubs	Negative
4.	Gottlieb, A. <sup>14</sup>	June 1944	55	M	Mexican	Farmer	Left foot	California	Wore shoes; no socks	Black	Maduromycoses Septate hyphae and clubs	Negative
5.	Twining, Dixon, and Weidman <sup>15</sup>	June 1944	42	M	American Italian	Soldier in 1918	Right foot	Pennsylvania	Injury	Grey white	Maduromycoses Monosporium Apiospermum	Proved by culture <sup>20</sup>
6.	Twining, Dixon, and Weidman <sup>15</sup>	1944	42	M	Filipino	Sailor	Right foot	Alaska	Bruised by cable	Black	Maduromycoses Cephalosporium granulomatus	Proved by culture <sup>20</sup>
7.	Hatch and Wells <sup>16</sup>	August 1944	54	M	Finn	Railroad	Right foot	Minnesota	Fractured twice	?	Actinomycoses	Negative
8.	Clough, F. E. <sup>17</sup>	December 1944	53	M	Mexican	Farmer	Left foot	California	No history	Brown	Actinomycoses	Negative
9.	Wood, D. A. <sup>18</sup>	March 1945	40	M	Filipino	Sailor	Left foot	Treasure Island	No history	Black	Not identified Pickled	No cultures
10.	Peters, J. H. <sup>10</sup>	March 1945	53	M	Negro	Ditch digger	Left foot	Louisiana	Stood in water	Yellow	Actinomycoses Nocardia asteroides actinomycoses	Proved by cultures
11.	Green, Bolton, and Woolsey	November 1946	35	M	Negro	Janitor	Right foot	Tennessee	Stepped on thorn	Ochroid	Actinomycoses Nocardia Madurac	Proved by cultures

## MYCETOMA—MADURA FOOT

In our review of the reported cases in this country, three were found to belong to Mycetoma Actinomycoses by the isolation of the causative filaments in pure culture and further study for their identification. The cases mentioned by Jones and Alden were those of Allison<sup>7</sup> in 1912, and of Lovejoy and Hammack<sup>8</sup> in 1920. Allison isolated an Actinomycete from his case in Texas of a Mexican gardener, and identified it as *Streptothrix Madura*. Lovejoy and Hammack sent their strain, recovered from a Mexican ranch laborer in California, to Boyd and Crutchfield,<sup>9</sup> who identified it a year later as *Actinomyces Mexicana*.

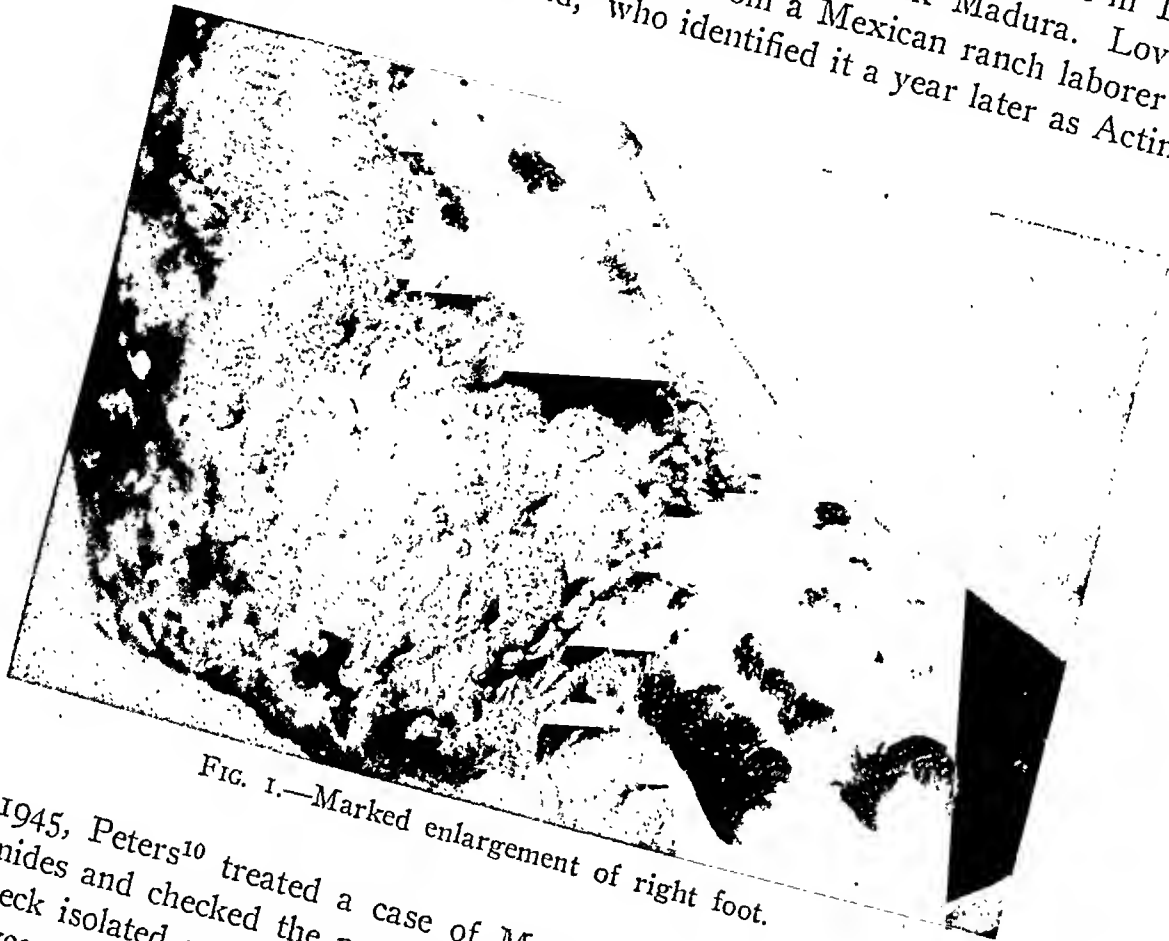


FIG. 1.—Marked enlargement of right foot.

In 1945, Peters<sup>10</sup> treated a case of Madura foot in New Orleans with sulfonamides and checked the progress of the treatment by cultures. Burns and Brueck isolated an Actinomycete from a case which they identified as *Actinomyces asteroides*. The case reported below represents only the fourth case in the United States which has been proven by cultures to belong to the *Actinomyces* group.

### CASE HISTORY\*

W. M., a 35-year-old colored male who had never been out of the United States, gave the following story. He lived in Memphis until late in 1944, at which time he moved to Chicago. He had never worked on a farm, but had done janitor work. The only antecedent history was that in 1925, while barefooted, and he remained on a thorn. Shortly thereafter the right foot became painful on motion, and he had no symptoms from 1925 to 1944, an interval of 19 years. Early in 1944, swelling of the foot appeared, and after persisting for several weeks, it subsided, and he was symptom free for 6 months. Swelling then again appeared, which subsided with rest, and about one year ago, a papule appeared on

\* This case was presented before the Chicago Surgical Society on November 1, 1946.

the dorsum of the foot; the papule broke down and a serosanguinous drainage was present. This subsided, but other papules appeared, until a great number of papules with draining sinuses were present, along with gradual but marked enlargement of the foot (Fig. 1) until finally he presented a foot, which because of its size, offered mechanical disability. There have been, and are, no subjective symptoms such as pain, fever, or systemic manifestations.

Physical examination upon admission to the hospital demonstrated a foot substantially as illustrated, with the exception that there was a serous drainage from many of the now covered papules. Blood picture and chemistry, repeated complement fixation tests, chest roentgenograms, and roentgenograms of other bones were all within normal limits. Roentgen-ray examination of the foot (Fig. 2, a and b) showed extensive destruction. It revealed numerous circumscribed, punched-out areas of radiolucency with deformity of the shafts of all the bones, and with destruction of the joint spaces. There was marked soft tissue swelling.

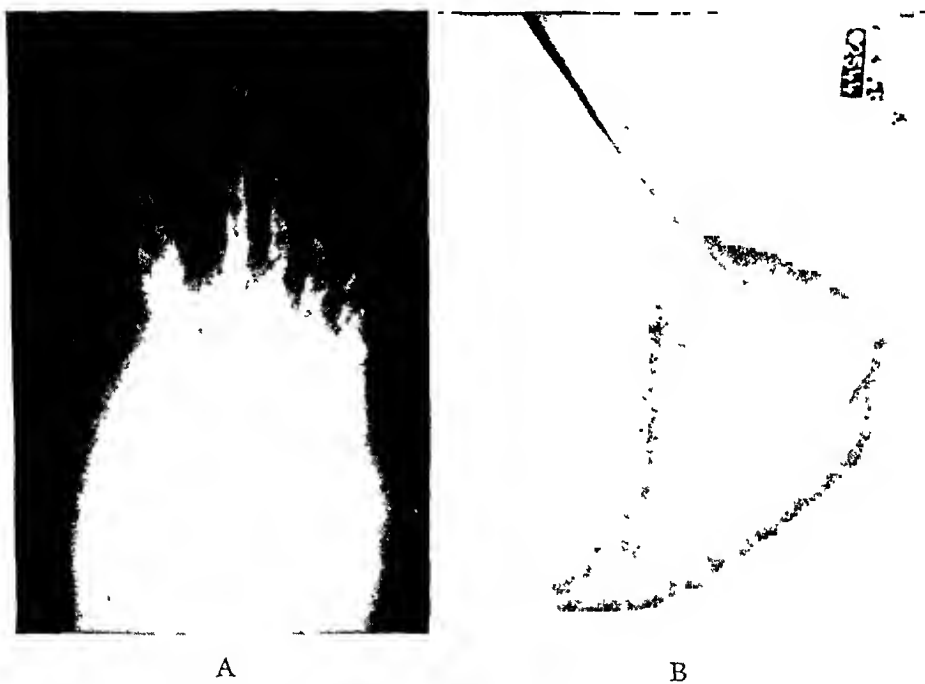


FIG. 2(A)—Extensive destruction of foot, as described in text.  
(B)—Extensive destruction of foot. Tibia and fibula appear normal.

*Bacteriologic studies.* Smears and cultures were made. The grains used for smears and cultures were removed surgically from the bases of the raised, moist papules that formed part of the characteristic appearance of the foot. This procedure was repeated upon 3 consecutive occasions so that cultures were started at intervals on Sabouraud's medium, both dextrose and maltose, and on Herrold egg yolk agar.<sup>11</sup>

The grains were pale or ochroid in color, hard and brittle. Smears, made by crushing and rubbing a grain between microscope slides, consisted of delicate nonseptate filaments less than  $0.5 \mu$  in diameter, and showed true branching (Fig. 3). The filaments were Gram negative containing Gram positive granules. They were not acid-fast. Grains were seen up to 3 mm. in diameter.

From none of the original cultures planted on the Sabouraud's media was growth of any kind recovered. However all the Herrold egg yolk agar cultures produced growth in varying degree by the tenth day. The colonies were tiny and brittle and all smears

# MYCETOMA—MADURA FOOT

FIG. 3

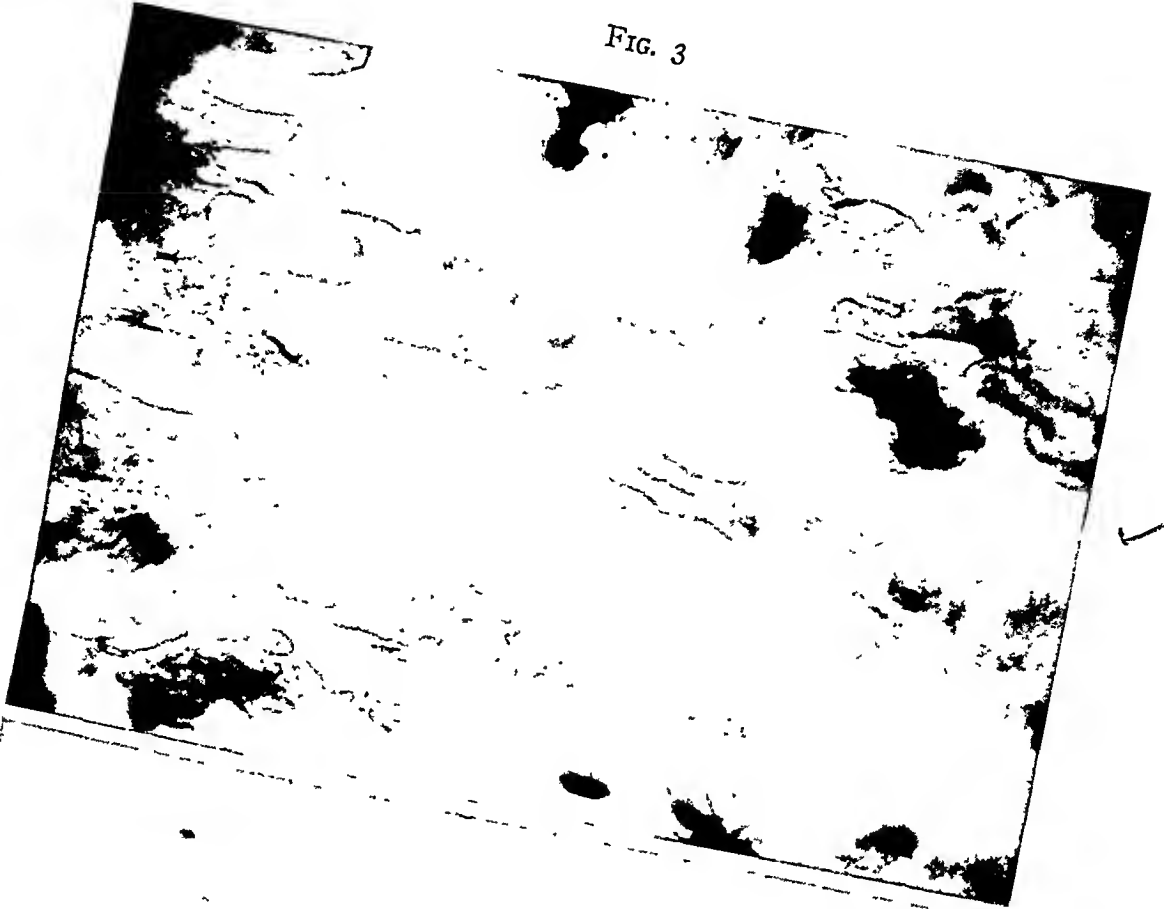


FIG. 4



FIG. 3.—Photomicrograph showing contents of a crushed grain from the sinus tract of the foot. Filaments were under  $0.5 \mu$  in diameter.  
FIG. 4.—Filaments of the same organism from a culture. Slender pointed Gram negative tips are numerous in the periphery of the cluster and Gram positive granules are noticeable in the older part of the filaments.

showed the same type of filament found in the original grain. The outstanding characteristics of these filaments from cultures were the long pointed ends definitely Gram negative without Gram positive granules near the tips (Fig. 4). They were under  $1\ \mu$  in diameter. Unusual forms were not found. In the tangle of the older filaments Gram positive granules were very noticeable. True branching was found occasionally.

The organism grew aerobically equally well at room and incubator temperatures. By subculturing the luxuriant growth from the Herrold egg yolk medium, new colonies were recovered in 6 days on blood agar, chocolate proteose agar, Loeffler's blood serum, and Herrold's egg yolk agar. Loeffler's medium was at no time liquefied. Growth was

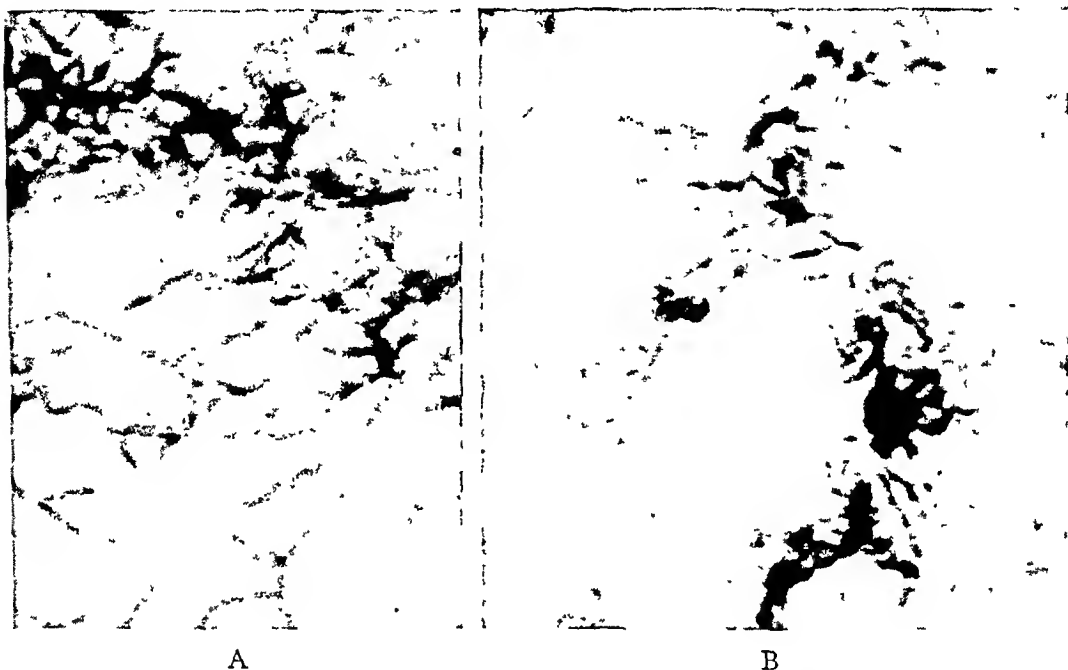


FIG. 5(A).—Gram positive club-like structures at the ends of faintly staining filaments. Special culture.  
(B).—Gram positive diphtheroids as found in many fields. Special culture.

recovered in plain broth as small pellets in the bottom and adherent to the sides of the tubes. In brain broth the pellets adhered to the surface of the pieces of brain. The broth did not become cloudy and filaments were not found in the smears. It was after the strain had been subcultured repeatedly on the egg yolk agar that generous transplants produced growth on both the dextrose and maltose Sabouraud's media.

The typical colonies were smooth, rounded and hard (Fig. 6), and did not produce aerial hyphae. They were hollow and grew tenaciously into the medium. Usually an entire colony or cluster of colonies was transferred for subcultures since they were too hard to break with a platinum wire loop. Occasionally a few tiny white flecks of aerial hyphae were noted on very old cultures where the medium had become paper thin. This hyphae consisted of strongly Gram positive filaments  $1.5\ \mu$  in diameter and varied in length, some reaching  $10\ \mu$ . No unusual forms were seen.

The ochroid color of the original grains prevailed in the majority of cultures on all media tried. However, on the Herrold egg yolk medium at times the young ochroid colonies soon turned into rich shades of coral, orange, or raspberry. Eventually young growth on Sabouraud's and Loeffler's media acquired the coral color. When the coral colored growth aged, it became a definite raspberry shade or a deep red. These colors were kept in stock by subculturing them on egg yolk agar, but they often reverted to the ochroid shade. At no time was the color absorbed by the medium.

## MYCETOMA—MADURA FOOT

While studying the colored colonies, smears and cultures were made from spreadable material obtained from the lining of one of the ball-like colonies of young coral growth on the Herrold medium. These cultures proved to be no different from others and the organism was still non acid-fast, but the long pointed tipped filaments (Fig. 4) were absent. Now, heavily Gram positive diphtheroids (Fig. 5b) were prominent as well as faintly staining filaments ending in Gram positive swellings or club-like structures (Fig. 5a). A few branched filaments were noted. The diphtheroids ranged in length from  $2\ \mu$  to  $7\ \mu$  by  $0.7\ \mu$  in diameter, while the club-like ends averaged  $1\ \mu \times 7\ \mu$  and varied in shape.

From the work accomplished to date, the organism isolated from this case of Madura foot belongs to the Actinomycoses group and is a strain of *Nocardia Maduræ*. Rabbits injected nine months ago with a suspension of the growth remained healthy. Further cultures are contemplated and an

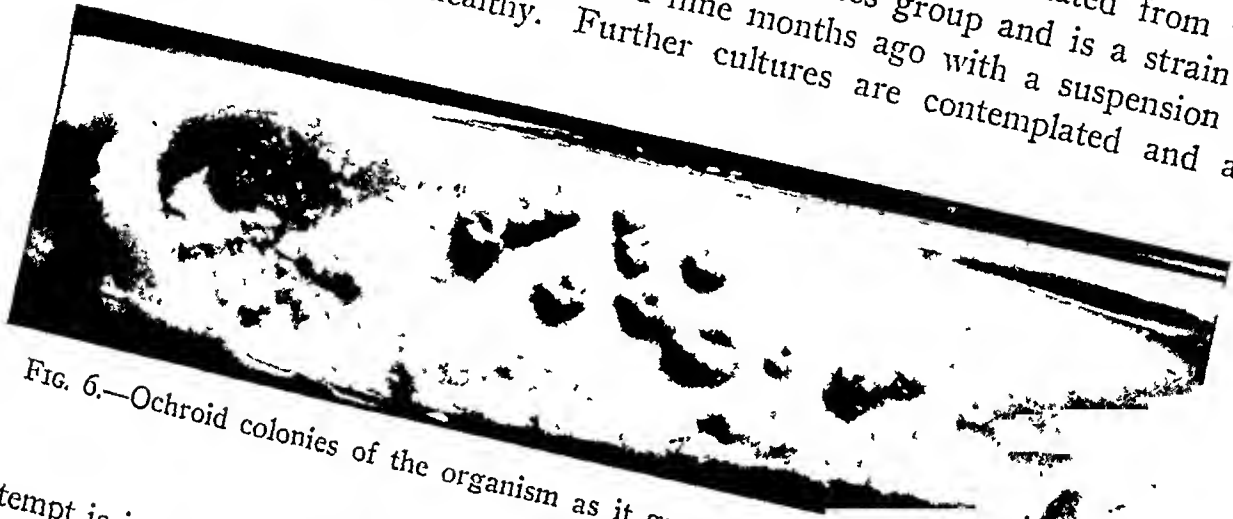


Fig. 6.—Ochroid colonies of the organism as it grows on Herrold Egg Yolk Agar.

attempt is in progress to find an explanation for the extreme hardness of the growth and for the source and variable appearance of the colors. We hope to submit a report upon these results at a later date. Our findings have been confirmed by Dr. C. W. Emmons, Principal Mycologist, National Institute of Health, Bethesda, Maryland.

On the basis of Peters' experience, previously mentioned, our patient received what we believed to be adequate amounts of sulfadiazine. Although the foot seems substantially free from infection, yet there has been no appreciable reduction in its size. Because of its bulk, it presents a mechanical problem to the patient, and it is felt that amputation will be resorted to.

It is possible that this entity may appear in the future among war veterans who will have been exposed to the etiological agents, and thus it is important to keep this condition in mind. It is probably most frequently confused with chronic osteomyelitis, chronic cellulitis, tuberculosis, and syphilis. It is possible that this condition is more prevalent than is generally assumed.

### SUMMARY

A case of Mycetoma-Madura Foot is described, proven by cultures, and representing, according to the literature reviewed, the fourth case in the United States which has been so proven. This actinomyces type is in contradistinction

to the more common type which is a true fungus. We have isolated the organism in this case in pure culture and have grown it on a variety of media, including Herrold's egg medium.

Madura Foot is a granulomatous condition resulting in marked deformity and enlargement of the foot, with destruction of the internal structures. There are nodules on the external surface which connect with granulomatous lesions of the interior of the foot by sinuses. These sinuses discharge granules of various sizes and colors, and it is from these granules that the organism is recovered.

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# VOLVULUS OF THE SIGMOID COLON\*

Report of Two Cases

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DUE TO THE RELATIVE PAUCITY of the reports in the American literature regarding volvulus of the sigmoid and the distressing lack of information in the usual reference books on the subject, we feel it pertinent at this time to give a brief discussion of the condition and to present two recent cases.

An interesting observation made while reviewing the literature was the fact that to 20 reports found in the American, British, and Australian literature 85 reports relative to volvulus of the sigmoid were found in non-English literature. A possible explanation for this fact is that the condition occurs with considerably more frequency in Russian and Baltic people than in British and American people.<sup>9</sup> It is of relatively common occurrence in Germany where it is reported to be the cause of large bowel obstruction in as high as 30 per cent of the cases. The percentages in this country are much less, but vary considerably. The condition is reported by Hinton and Steiner<sup>7</sup> to account for less than one per cent of acute intestinal obstruction and by Griffin, Bartron and Meyer<sup>13</sup> to be the cause of eight per cent of a series of 458 cases of large bowel obstruction at Cook County Hospital. Miller<sup>3</sup> reports it as the cause of 15 per cent of all forms of acute intestinal obstruction. (These are all American case figures.) An explanation for this inconsistency in percentages is perhaps the relative rarity of the condition. Few have been able personally to observe more than a small number of cases at most. An interesting explanation for the higher incidence of the condition in some other sections of the world, Russia and the Baltic area—for instance, is the dietary habits of these peoples. They seem to be more of vegetarians than we Americans, and their diet, consisting of coarser foods containing much cellulose, makes a greater demand upon the pelvic colon as a storehouse.<sup>9</sup> This might be conducive to a tendency toward redundancy of that part of the bowel.

## ETIOLOGY

There is general agreement that an enlarged colon and a redundant mesentery definitely predispose to volvulus; the former is usually present, and the latter invariably is found. A narrow attachment of the mesentery is listed by Hinton and Steiner<sup>7</sup> as a predisposing factor, but it seems that this is most likely a relative condition; since the attachment is a stable affair and cannot elongate commensurately with the mesenteric reflection at the bowel. Ligo and Overend<sup>9</sup> state that there is a familial tendency to congenital elongation of the pelvic colon and, hence, a predisposition to volvulus. There is

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general agreement that a history of chronic constipation is the rule. Heavy work and drastic purgation are suggested as precipitating causes.<sup>9</sup>

Volvulus of the pelvic colon is a disease of the older age group, most of the cases occurring in patients past the age of 40 years. It can occur in children—however, and Miller<sup>3</sup> reports a case occurring in a child 12 years old. Our two cases were 61 and 70 years of age respectively.

#### CLINICAL PICTURE

The history is that of acute low bowel obstruction. These patients usually are seen by a physician after one to several days of symptoms of partial or complete low bowel obstruction. The possible explanation for this is that it is the rule for these patients to have had several previous episodes of a similar nature which they have been able to relieve by means of purgatives and/or enemas without consulting a physician. This observation is substantiated by reports in the literature. Ligot and Overend<sup>9</sup> stress the importance of a history of diarrhea *after* the abatement of the cramping abdominal pains rather than *during* the pains. A history of chronic constipation is suggestive. It would be superfluous to reiterate the physical findings as regards the abdomen since they are those of acute low bowel obstruction from any cause.

The fluoroscope and roentgen-ray are important adjuncts in the diagnosis. Hall<sup>4</sup> lists three findings as his criteria for making a roentgen-ray diagnosis of this condition: (1) a tremendously dilated sigmoid colon situated predominantly in the right side of the abdomen, (2) valve-like obstruction distal to the dilation, allowing free entry of the enema fluid, yet preventing the patient from evacuating the contents from the dilated loop, and (3) normal mucosal pattern in the sigmoid distal to the dilated loop. Griffin, Bartron, and Meyer<sup>13</sup> found that 76 per cent of their patients were unable to take more than 500 cc. of enema fluid. A flat plate of the abdomen is of assistance when one observes a tremendously dilated loop of bowel rising out of the pelvis, frequently up as high as the liver, in the form of an inverted "U".<sup>9</sup>

A long history of repeated attacks is helpful in differentiating this condition from obstruction due to carcinoma, which runs a more progressive course.

#### TREATMENT

Once the diagnosis is made, the treatment is surgical—after the patient is properly prepared as regards fluid and electrolyte balance. Conservative surgery, in the form of fixation of the redundant bowel to the abdominal wall, was unsatisfactory in our hands as regards permanent relief of symptoms. This view is substantiated in the literature<sup>11</sup> by others who have performed this same conservative procedure. Likewise, mesentery-shortening procedures have been tried with the same poor results, and surgeons have been chagrined, when operating upon these patients for a recurrence following these conservative measures, to find no evidence of their painstaking efforts during the previous operation. This was our experience. It seems to be the consensus of opinion, and is our firm conviction, that the only rational treatment of

volvulus of the sigmoid is resection of the redundant bowel, preferably a Mikulicz resection. The lower mortality in the literature has been in the cases upon whom a Mikulicz resection was performed. Weeks<sup>2</sup> reports in a review of the literature up until 1931, 65 cases attended by a 33⅓ per cent mortality. Eighteen of these cases had a three-stage Mikulicz operation with but two deaths. Our experience was that the procedure is no more shocking than the more conservative surgery. Although occasional good results are reported in the literature of patients upon whom resection and primary anastomosis was performed,<sup>17, 16, 12</sup> we feel that the Mikulicz resection is less likely to be attended by complications such as might be experienced with primary anastomosis; in addition, the technical difficulty of uniting the dilated upper segment of the descending colon to the smaller distal portion sigmoid is great, considering the poor condition of the dilated bowel wall.

**Case 1. No. 4843:** White male 61 years of age admitted January 29, 1942, complaining of cramping abdominal pain, vomiting, and inability to pass flatus or feces. He remembered having a similar attack about a year previously, which abated spontaneously after 24 hours.

The examination was essentially negative except for a markedly distended abdomen with visible peristalsis. There was no muscle spasm. At this time a diagnosis of intestinal obstruction was made, and decompression by means of a Wangenstein suction was begun. The distention was not relieved by the next day at which time a barium enema was attempted. The barium was found to meet an obstruction after passing upward about six inches. During this procedure the obstruction was partially relieved, and a large quantity of liquid fecal material escaped, completely relieving the distention. Two days later the barium enema was repeated, and a partial obstruction was found at the recto-sigmoid junction. No growth could be visualized through the proctoscope.

On February 4, 1942, an exploratory laparotomy was performed, and no abnormalities of the abdominal viscera could be found other than a nodular liver and a somewhat dilated sigmoid with very redundant mesentery. It was estimated that the sigmoid could be elevated 12 to 16 inches outside the abdomen through the incision. The incision was closed with silk. The recovery was uneventful, and the patient was discharged on the tenth postoperative day, asymptomatic.

*Second Admission.*—Admitted February 26, 1945, with symptoms of low bowel obstruction. He was operated upon shortly after admission through a low, left paramedian incision, and a volvulus of the sigmoid was found. The volvulus was relieved manually; and the redundant sigmoid sutured to the abdominal wall on both sides of the incision with fine, interrupted cotton sutures. The wound was closed with interrupted cotton sutures. The patient was discharged on the seventh postoperative day.

*Third Admission.*—Admitted December 13, 1946, with symptoms of low intestinal obstruction of 18 hours duration. Two hours after admission the obstruction relieved itself spontaneously, and the patient was completely relieved of symptoms and began to pass flatus and feces. He was discharged asymptomatic the following day.

*Fourth Admission.*—He again reported on February 23, 1947, to the hospital with symptoms and signs of low bowel obstruction of 48 hours duration. After a short period of conservative efforts, with failure to relieve the obstruction, he was operated upon. This time a tremendously distended sigmoid colon was found, which was twisted upon itself and completely obstructed. No evidence of previous suturing of the bowel to abdominal wall was found. A Mikulicz resection was performed, about 18 inches of the sigmoid being thus resected. The incision was closed with interrupted cotton sutures. Two days later the clamps were removed from the ends of the divided bowel, and four

days after the clamps were removed (sixth postoperative day) a crushing clamp was applied.

Thirty-one days after the resection was performed the colostomy was closed. The skin sutures were removed seven days later, and the patient was discharged with normal bowel movements and no drainage from the wound.

**Case 2. No. 7613:** White male 70 years of age admitted to this hospital on December 6, 1946, complaining of abdominal distention of about 15 hours duration and inability to pass flatus or feces, despite purgatives and enemas. There was no nausea or vomiting. He gave a history of several similar episodes within the previous three years, which were relieved by enemas, but about which he had not consulted a physician. The remainder of the history was essentially non-contributory. An appendectomy was performed upon him in 1924.

The examination revealed a thin, white male appearing to be about the stated age with a very dry mouth and tongue. There were scattered moist rales over the base of the left lung, a markedly distended abdomen. The colon could be visualized throughout its course, and increased peristalsis could be auscultated throughout. No definite masses or localized tenderness were found. Rectal examination revealed no masses or obstruction within reach of the finger. The roentgen-ray of a barium enema showed the barium to stop about six inches up in the rectum, the blind end being of smooth outline. The diagnosis at this time was low intestinal obstruction, cause undetermined, and he was prepared for surgery.

Through a low, left rectus incision the abdominal cavity was opened, and an enormously distended sigmoid was found as the result of volvulus, which—when the torsion was relieved—was found to be quite atonic with an unusually long mesentery. The redundant sigmoid was sutured to the left lateral abdominal wall with interrupted sutures of fine cotton and the wound closed with interrupted cotton sutures. The patient was discharged on the fifteenth postoperative day in good condition.

*Second Admission.*—Since being discharged from the hospital about two and one-half months before, the patient had enjoyed good health until 24 hours before admission. He began to experience cramping abdominal pains, to notice that he was becoming distended, and was unable to pass flatus or feces.

The physical examination was essentially the same as on the previous admission. He was again prepared for surgery.

The operative findings were essentially the same as on the previous occasion with no evidence of the colon having been sutured to the abdominal wall. The volvulus was relieved and a Mikulicz resection performed. The clamps were removed from the cut ends of the bowel two days later and a spur clamp applied on the sixth postoperative day.

Four weeks postoperatively the colostomy was closed. His subsequent course was uneventful except for a fecal fistula at the site of the closure which closed spontaneously before his discharge on the fifty-first postoperative day.

This patient has remained asymptomatic.

#### COMMENT

Judging from the reports in the literature volvulus of the sigmoid is of relatively infrequent occurrence, but it is common enough that every surgeon should familiarize himself with the pros and cons as regards conservative and more radical surgery. From our experience with these two very similar cases and from the information gleaned from the literature, we are of the opinion that a resection of the Mikulicz type at the initial operation is the operation of choice and that it is very little—if any—more shocking than the more conservative procedures. In each of these cases the patient might have been spared the added expense and inconvenience of more than one admission for the

same condition, had this view been taken at first. Of course, the follow-up is not of sufficient duration for one to make any conclusive statements as regards the permanency of the present freedom of symptoms, but—anatomically—one would expect it to be more successful than the more conservative surgery which was in our hands.

#### SUMMARY

A brief discussion of volvulus of the sigmoid colon is given. Two cases are presented of recurrent volvulus of the sigmoid following conservative surgery, which subsequently required partial sigmoidectomy for the relief of symptoms.

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# GASTRODUODENAL INTUSSUSCEPTION\*†

## A CASE REPORT

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SIMPLE PROLAPSE of the antral mucosa through the pylorus, with or without associated gastric polyps is quite common, but actual intussusception of all coats of the stomach wall is very rare.

Intussusception of the degree encountered in the case described below is almost a medical curiosity.

## CASE REPORT

H. N., No. 44987. The patient was a dental assistant, 35 years of age, who was admitted to the Roosevelt Hospital for the first time on July 29, 1947. She complained of well localized epigastric distress of about three months duration. The initial symptom had been a puzzling and persistent eructation of gas and sour liquid after meals, associated with a feeling of distention and pressure in the upper abdomen. As the weeks passed, despite numerous modifications in her diet, the discomfort became more accentuated. During the early days of her illness, small doses of bicarbonate had given some relief, but after a while it induced vomiting and the patient discontinued its use. At the time of entry into the hospital, she was nauseated most of the time. Although there had been no lack of appetite, she had practically stopped eating because food immediately aggravated the discomfort and was promptly regurgitated. During the preceding two months she had lost 12 pounds in weight. No gross bleeding had been observed and the patient had not noticed any discoloration of the vomitus or of the stools.

Her past history failed to disclose any previous attacks of a similar nature. As a matter of fact, she had never been disturbed by gastro-intestinal symptoms of any sort except for a very rare attack of diarrhea.

On physical examination there had been obvious weight loss. Blood pressure, pulse, respirations and temperature were normal. There was a distinct pallor but no jaundice or cyanosis. No cervical lymph nodes were palpable. The heart and lungs were entirely normal. Examination of the abdomen revealed only slight mid-epigastric tenderness and a sense of fullness in the mid-epigastrium without any definite mass. The extremities and reflexes were normal.

Within a few days after admission a gastro-intestinal series was done (Figs. 1 and 2) and the following findings were noted. The esophagus was normal. There was a large gastric defect involving the fundus and antrum with distortion of the duodenal bulb. There was lack of filling of the descending duodenum without any delay, however, in the emptying time of the stomach.

Lateral views showed essentially the same picture, with what appeared to be forward displacement of the stomach and antrum.

The diagnosis lay between a large benign intragastric tumor or a large primary tumor of the pancreas producing a pressure defect in the antrum and fundus. A gastroscopic examination was not permitted by the patient.

Following additional clinical studies, all of which failed to provide any further diagnostic assistance, operation was performed on July 14, 1947.

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† Presented before the New York Surgical Society on February 25, 1948.



FIG. 2.—Lateral oblique view.



FIG. 1.—Antero-posterior view of stomach and duodenum following ingestion of barium.



FIG. 3.—Gastroduodenal intussusception as found at operation.

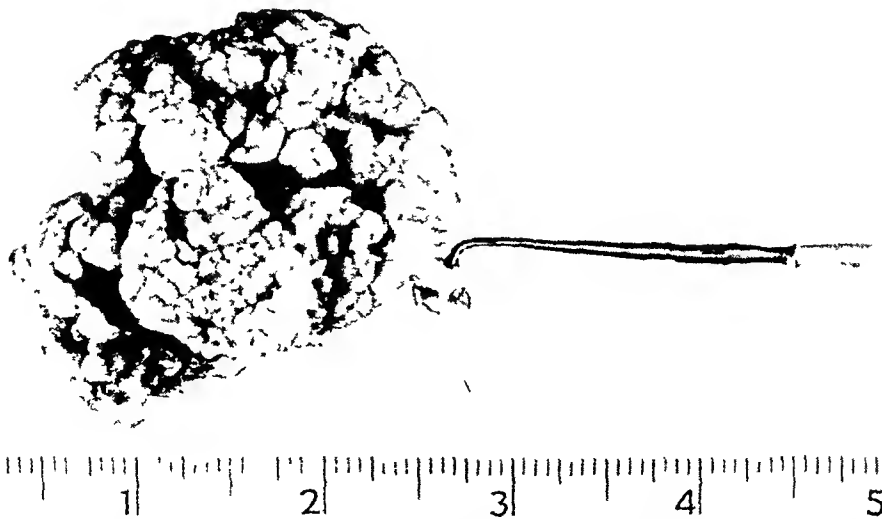


FIG. 4.—Gastric polyp removed at operation. The hook indicates the pedicle of the tumor.

The situation found at operation is illustrated in Figure 3. About two thirds of the stomach had herniated through the pylorus into the duodenum. As a result of this intussusception, the duodenum was dilated to about three inches in diameter down to the region of the duodenojejunal flexure. Although the pyloric muscle was still fairly tight, the intussusception was reduced without too much difficulty. As the stomach was delivered through the pylorus, a soft tumor was felt springing up through the pyloric ring as though attached to a large rubber band. Palpation of the stomach then revealed a mass about the size of a billiard ball within the gastric cavity. A long

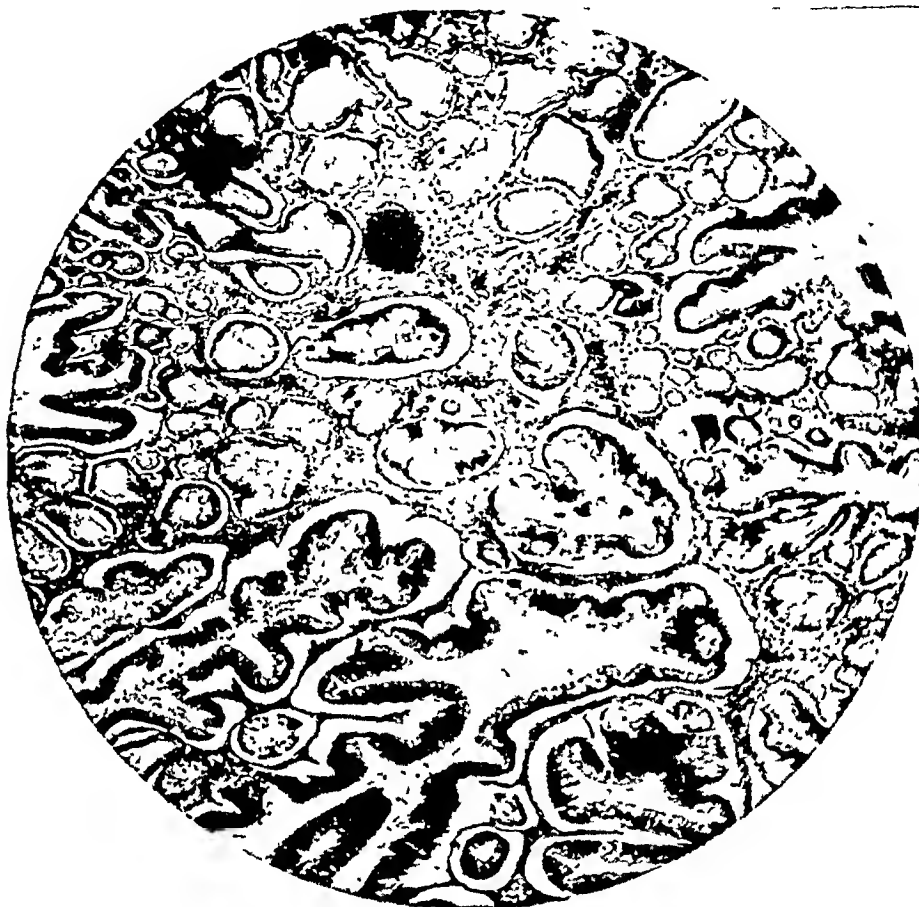


FIG. 5.—Microphotograph of one of many sections made through various parts of the tumor.

gastrotomy was performed and a soft spongy tumor was found attached by a pedicle one inch long to the upper posterior third of the stomach wall. Since the tumor looked and felt benign, and the pedicle was obviously not involved, a simple removal of the tumor was performed by elliptical incision around the base of the pedicle. The resulting defect was closed with interrupted sutures of fine silk. Inspection of the gastric cavity failed to reveal any other polyps. The gastrotomy was then closed with two layers of interrupted Halsted sutures. The abdominal wound was closed in layers.

Figure 4 shows the tumor as removed, and Figure 5 is a microphotograph of one of the many sections from various portions of the tumor.

Microscopic examination showed simple benign adenomatous polyp.

The patient made a smooth recovery and has been entirely free of symptoms since operation.



# CHOLECYSTITIS DUE TO GIARDIA LAMBLIA IN A LEFT-SIDED GALLBLADDER\*

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THERE HAVE ONLY BEEN seven reported cases of infection of the gallbladder due to giardia lamblia in the literature to date. However, there is increasing evidence that this protozoa is the causative factor in cholecystitis more frequently than the rarity of reports would indicate. The case herein reported was one in which giardia were proven to be the cause of infection in a gallbladder. It is all the more unusual since the gallbladder was found to be situated on the left side. The giardia lamblia was found repeatedly on duodenal drainage. The organism promptly disappeared under treatment with atabrine. The cystic form was recovered from the gallbladder after surgical removal. This is the eighth reported case of giardiasis of the gallbladder, and probably the second in which cysts were found in the gallbladder.

Leuvenhoek<sup>10</sup> first discovered giardia in 1681, in a specimen of his own stool. The organism was rediscovered and named by Lamb<sup>5</sup> in 1859. It is a protozoa measuring 8 to 20 mu. long and 5 to 12 mu. wide. In other words, it is larger than a red blood corpuscle, and smaller than an epithelial cell. It contains four ventrally placed flagellates, and is actively motile. It is a common inhabitant of the gastro-intestinal tract, and was formerly considered non-pathogenic. Its pathogenocity, particularly in the case of diarrhea, has been definitely established. Berberian<sup>1</sup> reviewed the reports of 15 authors on the pathogenocity of giardia lamblia with reference to diarrhea. Several of these authors definitely established it as the causative organism in epidemics of diarrhea, particularly in the Middle East. Routine examination of stool specimens in this country and abroad showed that the highest incident of giardia lamblia occurred in areas where sanitation was at its lowest. In Puerto Rico, 48 per cent of the population were found to be infested. A study of Chicago dispensary patients revealed a rate of only 1.66 per cent; while in Tennessee the rate was much higher at 14.7 per cent.

While proven cases of infection of the upper gastro-intestinal tract with this parasite have not been so common as those in connection with diarrhea, there is increasing evidence that the organism produces gallbladder disease,

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and probably more frequently than has been supposed. Smithies<sup>11</sup> claimed to be the first to report a case of giardiasis of the gallbladder. He found the protozoa in a gallbladder which had been removed by the late Dr. A. J. Ochsner of Chicago in December, 1917. He later reported a second case.

Keyes<sup>9</sup> reported two cases of cholecystitis, in one of which he found cysts of giardia in the gallbladder. Hartman,<sup>8</sup> in 1942, in a review of the literature, found reports of only four cases of giardiasis of the gallbladder. He added a case of his own, however, he omitted the two cases of Keyes. Search of the literature since that date has failed to reveal any reports of proven cases. Reported cases to date of cholecystitis due to giardia lamblia may be summarized as follows:

Smithies.....	2 cases
Westphal and Gerogi <sup>13</sup> .....	1 case
Calder and Ridgon <sup>3</sup> .....	1 case (autopsy)
Hartman.....	1 case
Keyes.....	2 cases
<hr/>	
Total.....	7 cases

Another indication of the pathogenocicity of the giardia lamblia in relation to the upper gastro-intestinal tract is the increasing number of reports in the literature showing the frequency with which it is found in duodenal drainage in association with symptoms simulating disease of the gallbladder or duodenum. Wesselman<sup>12</sup> reported two cases presenting symptoms simulating cholecystitis in which giardi were found on duodenal drainage. Prompt and complete relief was obtained by administration of acranil. DeMuro<sup>4</sup> reported a series of 45 cases in which he recovered giardia from the bile obtained on duodenal drainage. Of these, 31.1 per cent suffered from upper gastro-intestinal symptoms which he referred to as "entero-hepato-biliary syndrome." Goss<sup>5</sup> examined the stools of 300 patients for giardia, and found this protozoa to be present in 9 per cent. However, more interesting is the fact that in those suffering from symptoms simulating ulcer or gallbladder disease, the instance was 34 per cent. He believes that giardiasis leads to vitamin deficiency.

For the treatment of giardiasis, atabrine is a specific; although good results have been reported with other forms of therapy. Boros<sup>2</sup> treated a case of giardiasis of the duodenum simulating ulcer with five injections of 0.45 Gm. neosalvarsan at five-day intervals with good results. Goss<sup>5</sup> recommends, among other things, carbarsone. Berberian<sup>1</sup> found acranil 100 per cent effective in eliminating this infection in cases of stool contamination. The recommended dosage is as follows:

Age 3-6	0.1 Gm. per day for five consecutive days
7-12	0.1 Gm. twice daily for five consecutive days
13-16	0.1 Gm. three times daily for five consecutive days
Over 16	0.5 Gm. per day for the first day, and then 0.1 Gm. three times daily for four more days.

Hartman<sup>8</sup> and associates obtained a cure in their case of giardiasis of the gallbladder with atabrine in doses of 0.1 Gm. three times daily for five days.

Gross<sup>6</sup> reviewed the literature on *gallbladder anomalies* thoroughly in 1936, and was able to find only seven cases of left-sided gallbladder. In each case the vesicle was situated in the under surface of the left lobe of the liver. The gallbladder was usually found to be normal in size. The cystic duct joined the common hepatic duct in the normal manner and position in three cases, the left hepatic duct in one and unrecorded in three. The embryologic development of this anomaly may occur in one of two ways. The gallbladder anlage begins as a normal embryologic bud from the hepatic diverticulum and migrates to the left where it becomes fixed by the developing peritoneum to the under surface of the left lobe of the liver. This accounts for the normal entrance of the cystic duct into the hepatic duct. This was the situation in cases described by Harris and Walton.<sup>7</sup> They described the cystic duct as coming off at the normal site extending forward and to the right in the direction of the normal site of the gallbladder and then making a sharp hairpin turn to join the fundus under the left liver lobe. The second way in which this anomaly may develop is as follows: A gallbladder develops on each side with one persisting on the left and the right-sided one becoming atrophic and disappearing. In such a case one would expect the cystic duct to drain into the left hepatic duct as has been reported in one case.

### CASE REPORT

W. E. S., a white male, age 18, was admitted to Regional Hospital, Camp Joseph T. Robinson, on February 15, 1946. His *chief complaint* was pain in the right side of the abdomen of three days' duration. His *past history* was irrelevant, except for an appendectomy in 1944. He had not seen tropical service.

*The history of the present illness* revealed that three days prior to admission he developed pain in the right upper quadrant of the abdomen in the subcostal region. Pains had been sharp enough to "shut his wind off." Pain radiated to the left side, but not to the shoulder or directly to the back. He vomited twice. Vomitus contained food which he had previously eaten. Stools were normal in appearance and contained no evidence of blood. There was no history of intolerance to food.

*Physical examination* revealed a white male in a good state of nutrition. The temperature was 98; pulse 84; and respiration, 22. The abdomen was tender on palpation in the right upper quadrant. The liver was not palpable. The blood pressure was systolic 110, diastolic 60. Physical examination was otherwise negative.

*Laboratory Tests and Special Examinations:* Routine blood tests and urinalysis were within normal limits. The serum protein was 7.5; blood cholesterol, 1.36; and the blood Kahn was negative. The sedimentation rate was 7; hematocrit, 44; icteric index, 10.2. Examination of the bile obtained on duodenal drainage on March 8, 1946, showed *numerous giardia lamblia* present. These protozoa were clumped together in small rod-shaped structures, as if they had formed casts of the small radicles of the biliary tree. They were packed solid in these casts and occasionally one would break away from the general mass and swim in the fluid media.

*X-ray examination* of the gallbladder (Graham series) taken on February 20, 1946, showed no evidence of filling. Both kidneys appeared normal, and intravenous pyelograms were within normal limits. Roentgen examination of the upper gastro-intestinal tract failed to reveal any other pathology.

*Course in Hospital:* On March 7, 1946, the patient was put on daily duodenal drainage. Because of the repeated finding of giardia in the bile, administration of atabrine was begun, on March 16, 1946, in doses of 0.1 Gm. three times a day. This therapy was



FIG. 1.—This is a drawing from the microscopic examination of the bile obtained on duodenal drainage. In the upper left-hand corner is a mucous cast containing numerous giardia. This cast probably came from one of the small radicles of the biliary tree. In the lower right-hand corner is a high power of the organisms.



continued for one week at the end of which time the giardia had disappeared from the duodenal drainage. None were found subsequently from repeated drainages taken almost daily between March 26 and May 9. A second roentgenogram of the gallbladder showed no evidence of filling with the contrast media (Priodax). The cephalin flocculation test on March 5 was as follows: 24 hours plus and minus; 48 hours plus and minus. Examination of the feces on three successive days, starting on March 25, showed no evidence of parasites. The patient was operated upon April 5, 1946, at which time the gallbladder was removed and the common bile duct explored and drained.

*The operative findings were as follows:* Gallbladder was situated under the left lobe of the liver. The fundus was the same distance to the left of the falciform ligament as the

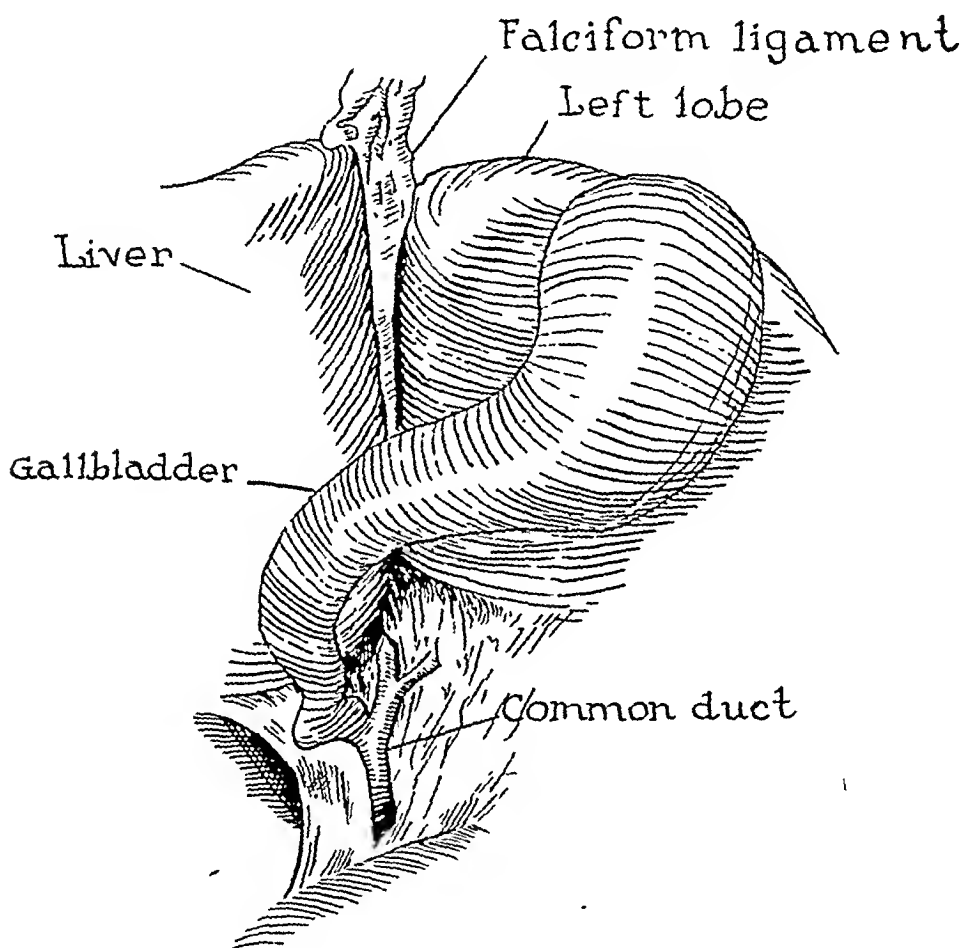


FIG. 2.—This is a diagram of the anomalous gallbladder in which the fundus was situated in the left lobe of the liver. The neck of the gallbladder crossed over to the right crossing the longitudinal fissure near its posterior end. The cystic duct joined the common duct on the right side.

normal gallbladder is usually to the right. The neck of the gallbladder crossed over to the right, crossing the longitudinal fissure near its posterior end. The cystic duct joined the common hepatic duct on the right side. The common bile duct, pancreas and other organs were essentially normal. The liver showed evidence of considerable hepatitis. It was moderately swollen and there were visible areas of fibrosis. These areas of fibrosis radiated over the surface of the liver substance from the gallbladder. There was further evidence of cholecystitis in the form of edema about the cystic duct and adhesions to the duodenum. No stones were found in the gallbladder or common bile duct. A T-tube was placed in the common bile duct for the purpose of subsequent study of the bile for evidence of giardia infection.

*Pathologic Examination* of scrapings of the gallbladder mucosa showed the presence

of giardia cysts. There was also evidence of ulceration in the mucosa of the gallbladder extending into the submucosa.

*Postoperative Course:* Patient made an uneventful convalescence. Repeated examinations of T-tube bile and also of duodenal drainage postoperatively were negative for giardia. The T-tube was removed at the end of six weeks. Patient has since been symptom free. Cholangiograms taken on May 1, 1946, showed the common duct and biliary tract to be normal.

*Comment.* This is a case of a man with left-sided gallbladder with typical symptoms of cholecystitis in whom giardia lamblia were found in large quantities in the bile obtained on duodenal drainage. These protozoa promptly disappeared following administration of atabrine as did the symptoms. Besides roentgen evidence, the gallbladder showed signs of inflammation at the operating table and giardia cysts were found in the gallbladder wall after surgical removal.

### DISCUSSION

The evidence in favor of this being a giardia infection rather than an infestation is: (1) typical symptoms and physical signs of cholecystitis relieved by atabrine; (2) failure of the gallbladder to cast a shadow on the x-ray film after a Graham series on two occasions both before and after repeated duodenal drainages; (3) findings at the time of operation of streaks of fibrosis on the liver surface extending from the gallbladder and inflammatory reaction around the cystic duct; (4) pathologic study of the gallbladder showing ulceration in the mucosa and submucosa and the finding of giardia lamblia cysts in the scrapings of the mucosa.

### SUMMARY AND CONCLUSIONS

1. While giardia lamblia in the past has been considered harmless there is increasing evidence that it is capable of producing gastro-intestinal disease.
2. Only seven proven cases of gallbladder disease from giardia have been previously reported in the literature; however, there have been instances of cases with symptoms simulating gallbladder disease or duodenal ulcer in which giardia lamblia were found in the bile obtained by duodenal drainage. Alleviation of symptoms was obtained by elimination of the protozoa by therapy.
3. Although various forms of therapy have been recommended, atabrine appears to be the drug of choice. The recommended adult dose is 0.1 Gm. three times daily for five days.
4. A case of giardiasis in a patient with a left-sided gallbladder is herein reported. In this instance the giardia were found in the bile obtained by duodenal drainage. They were eliminated by administration of atabrine and symptoms promptly subsided. When the gallbladder was subsequently removed, giardia cysts were found in the gallbladder wall.

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[Signed] J. R. ARNOLD.

Affirmed to and subscribed before me this 7th day of October, 1948.

[Seal]

HARRY J. BEARD.

(My commission expires March 5, 1949.)



# MEDIASTINAL LIPOMATA: A CASE REPORT\*

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LESS THAN 50 intrathoracic lipomas have been reported. Seventeen of these have been successfully excised.<sup>1, 2, 3, 4, 5, 6</sup> Heuer and Andrus, in the first comprehensive report<sup>1</sup> in 1933, suggested three anatomic groups: the hour-glass tumors, in which part of the tumor lay within the thorax and the remainder penetrated the intercostal structures to present subcutaneously; the superior mediastinal lipomas which present at the root of the neck; and the entirely intrathoracic lipomas. The majority occupy the mediastinum. The disease is a rare clinical entity and therefore the following case is considered worthy of report.

## CASE REPORT

E. M., a 30-year-old negress, had a routine chest roentgenogram in 1945 which showed a superior mediastinal mass. She was asymptomatic and did not seek medical aid. Another roentgenogram in 1947 revealed the mass with moderate increase in its size although she was still asymptomatic. She received four radiation treatments without any reduction in the size of the mass. The patient was then referred to one of us (E. H. G.) who advised surgery.

She entered the Methodist Hospital, Brooklyn, on November 3, 1947. History and physical examination were completely negative. Laboratory studies were negative with the exception of roentgenograms of the chest (Fig. 1) which showed an ovoid tumor mass anteriorly in the superior mediastinum, considered to be a dermoid or a lipoma.

On November 5, 1947, anterior thoracotomy was performed by the senior author through the second left intercostal space. The mediastinum was entered transpleurally. A grapefruit sized fatty tumor was found overlying the heart and aorta within the mediastinal pleura. A projection from the main mass extended up through the superior thoracic aperture into the neck (Fig. 2). The tumor which was well encapsulated was removed without difficulty. The lung was re-expanded by means of positive intratracheal pressure and the chest was closed without drainage.

The hospital course was uneventful and the patient was discharged on the ninth postoperative day.

The pathologic report was lipoma.

Follow-up chest films showed expansion of the lung and absence of mediastinum mass density.

## DISCUSSION

Although the correct diagnosis was suspected preoperatively in this case, surgery is indicated in all mediastinal tumors. It is the only means of positive

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\* Submitted for publication May, 1948.

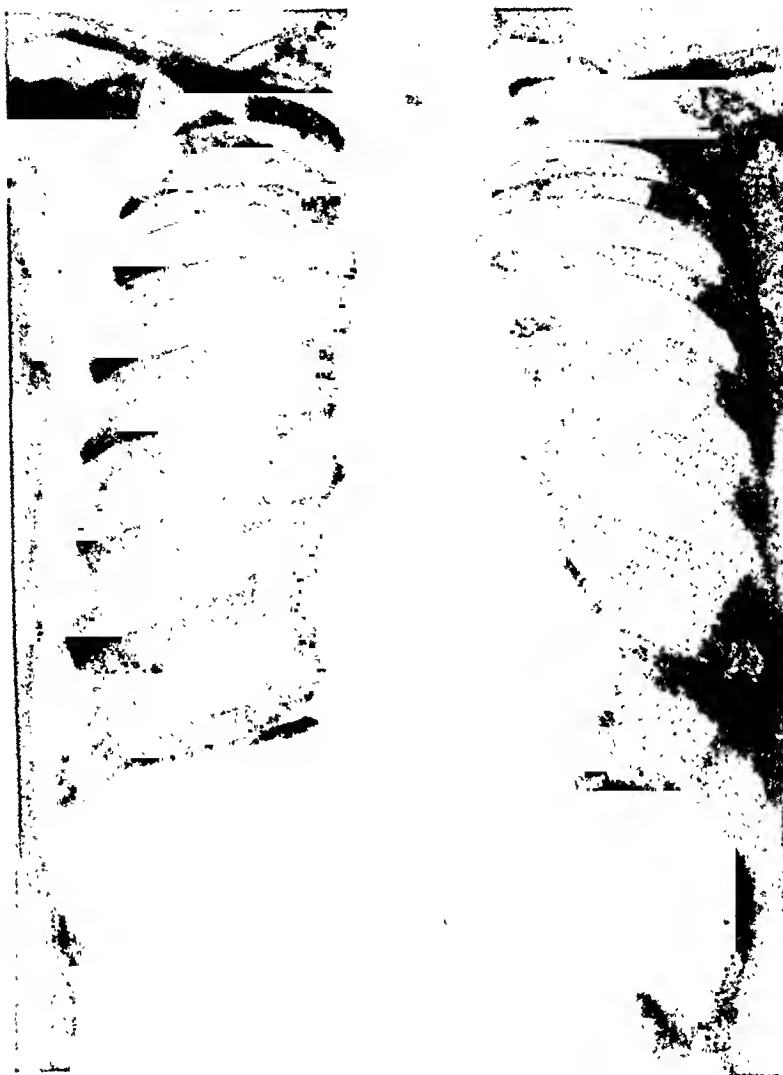


FIG. 1.—Preoperative roentgenogram of the chest.



FIG. 2.—Photograph of tumor (cut surface).

diagnosis in the non-lymphomatous types. Moreover, it is the only definitive therapy. There is futility and danger in giving radiation therapy to mediastinal tumors of unknown nature. The too common practice of employing a "test dose" of deep roentgen ray therapy may erroneously place the label of malignant lymphoma on a patient whose prognosis is, in reality, more favorable. The majority of cases of Boeck's sarcoid show mediastinal node involvement and this often simulates roentgenologically other mediastinal tumors. Many of these shadows show regression or even complete disappearance under observation.<sup>7</sup> Radiation therapy, in this period, would lead to a faulty diagnosis and prognosis. It is equally true that valuable time may be lost with radiotherapy and a once operable tumor become inoperable. Thus a patient's "day of grace may be sinned away" with a modality which is not curative. Pathologic diagnosis should be reached by thoracotomy which, in properly selected cases, is a safe procedure.

In the second place, even if it were known definitely that the tumor was a lipoma, it is probable that pressure symptoms would eventually manifest themselves and make surgery mandatory. That lipomata may attain tremendous size is well illustrated by Heuer's case in which the tumor filled the entire left hemithorax. Death from pressure has been reported.<sup>1, 2</sup> Thirdly, malignant degeneration or infection must be considered as possible complications.

Exploration through the anterior intercostal route without division of ribs gave adequate exposure in this case and, we feel, a more comfortable convalescence to the patient.

#### CONCLUSIONS

Mediastinal lipoma is a fairly rare disease. The treatment is surgical. The futility of giving radiation therapy to mediastinal tumors of unknown nature is stressed.

#### SUMMARY

A case is presented in which a lipoma was successfully removed from the anterior superior mediastinum.

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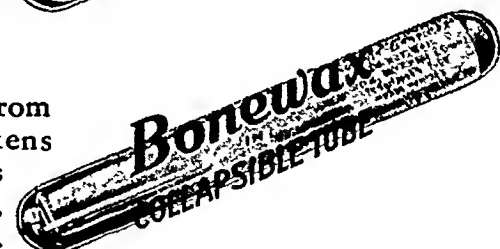
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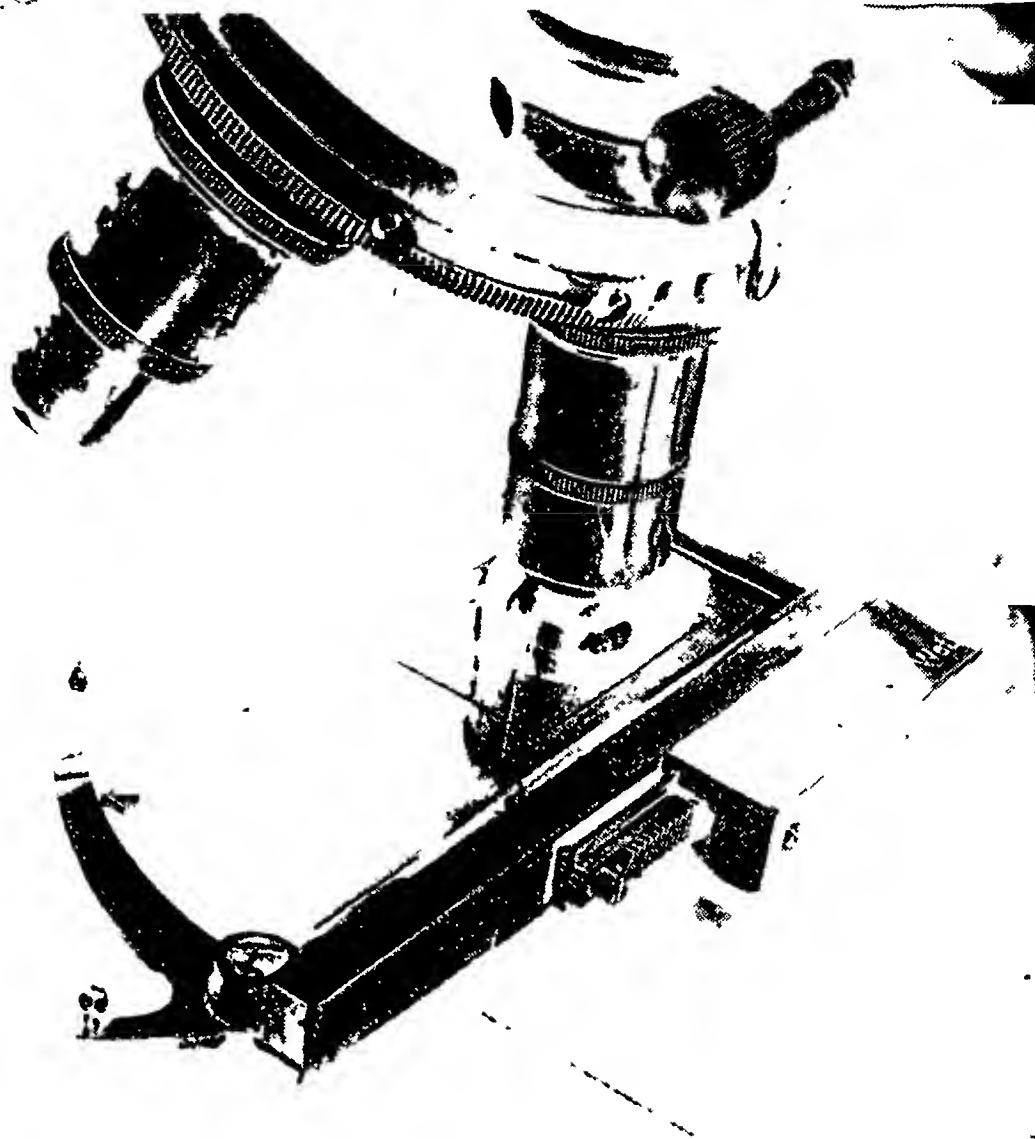
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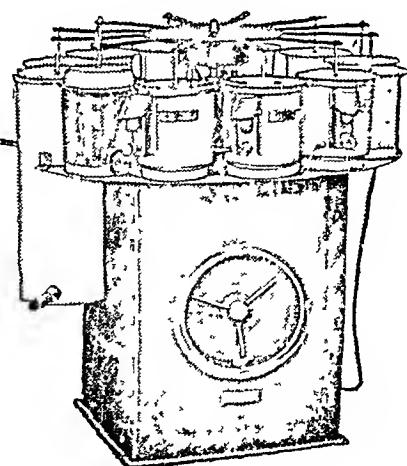


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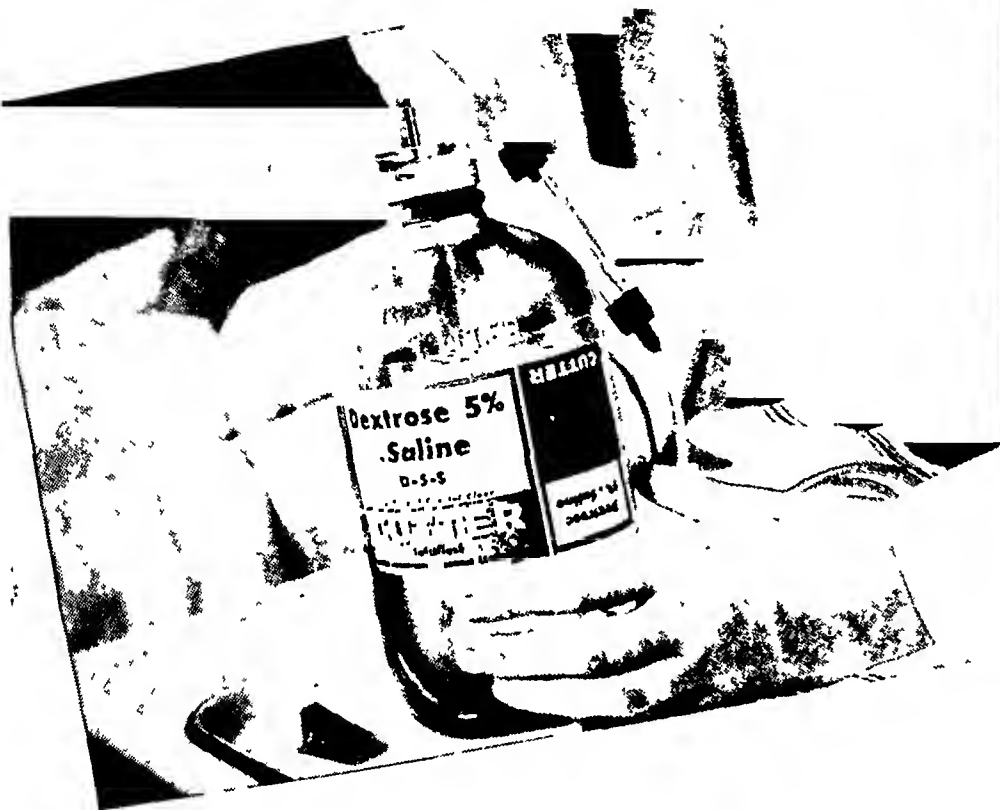
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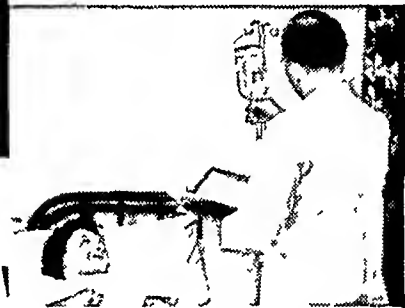
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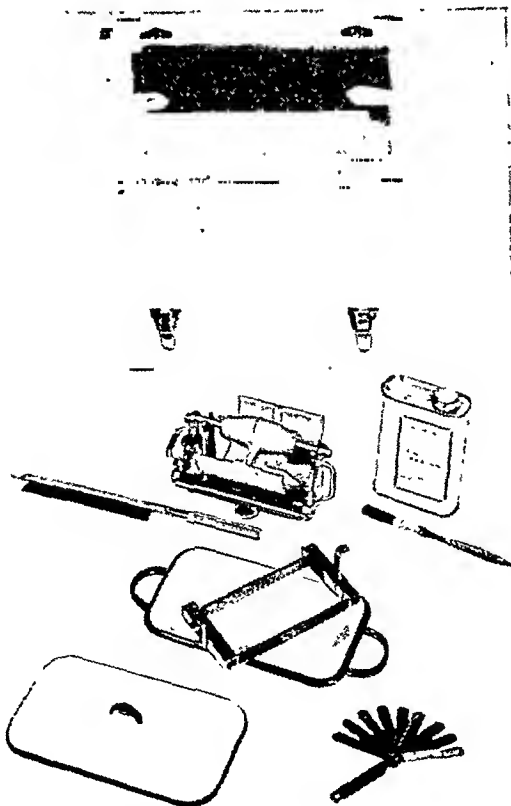
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## THE NATURE OF THE SHIFT OF PLASMA PROTEIN TO THE EXTRAVASCULAR SPACE FOLLOWING THERMAL TRAUMA\*†

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DISCUSSION of the circulatory disorder of the burned patient and of the need for fluid to survive is inadequate if it does not include a consideration of the abnormal distribution of the plasma proteins occurring within the body as the direct result of the injury. In the burned, as in the healthy, it is the colloid osmotic pressure exerted by the plasma proteins in differential concentrations on either side of the semi-permeable capillary membrane which appor- tions water between plasma and interstitial space and maintains blood pressure. It is the sudden increase in permeability of the capillary caused by the burn which destroys the osmotic pressure of the plasma in the area of injury and permits the collection of edema in the wound.

Two misconceptions regarding the distribution of plasma protein are current. First, it is believed that the proteins of plasma circulate only within the blood stream. On the contrary, the normal capillary membrane is incom- pletely restrictive; albumin, and to a lesser extent globulin, pass out in small concentration from the plasma into the interstitial fluid. The experiments of Drinker on the lymph of dogs, and of others, have made this clear.<sup>1</sup> The lymph protein, and therefore presumably that of the interstitial fluid, varies from less than 1 per cent in the superficial tissues of an extremity to as much as 5.0 per cent in the liver. Though data are limited in the human being to thoracic duct lymph and various edema fluids, it is reasonable to expect that comparable quantities of protein will be found in man outside of the blood vessels. Since

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the protein outside the vessels is still in circulation, eventually reentering the venous blood via the lymph channels, such protein must be taken into account when estimating protein requirements and water distribution in the burned patient.

The second misconception deals with the change in concentration of protein in the plasma following the burn. Because plasma protein has been proved to leak out of the capillary into the wound it has been stated repeatedly that the remaining plasma has a lowered protein concentration. The reverse is true. The lowered protein concentration found some hours after injury is a secondary phenomenon, the result either of withdrawal of water from unburned tissues, or therapy, or of both.

Because an understanding of the redistribution of water and electrolytes is essential in the care of the burned patient, an account is given of the observations, both experimental and clinical, made by the group studying burns at the Massachusetts General Hospital, bearing on the nature of the shift of protein following a burn.

#### EXPERIMENTAL OBSERVATIONS

The disordered distribution of protein as a result of a burn has been approached experimentally by collecting lymph flowing from the burned foot of the dog. The abnormal flow of lymph engendered by the burn indicates the volume of water passing through the wound, while the discrepancy in protein between the circulating plasma and lymph indicates the permeability of the capillary to protein. The nature of the water and protein leakage from the plasma and the effect of the leakage upon the residual plasma have been examined. Abnormal proteins have also been searched for.

*Lymph Flow and Protein Leakage.* The experimental method used is that of Drinker. Field, Drinker and White in 1932<sup>2</sup> described an increased flow of water and protein from capillary to lymphatic trunk through an area of sterile inflammation induced by a burn. The foot of a dog was burned by immersion in hot water. The lymph was collected through a cannula placed in a lymphatic trunk above the ankle. Following the injury the protein concentration rose from the normal of 2 Gm./100 cc. to nearly 4 Gm. The flow initially increased by the heat, returned after two and a half hours to that before injury. This classic observation, by measurement of lymph flow and protein concentration, of abnormal capillary filtration in a burn wound of the foot of the dog has been amply confirmed in further work by Drinker and his collaborators,<sup>3</sup> and by ourselves.<sup>4</sup> Evidence of increased flow in the lymphatics in burns has also been obtained by McMaster in smaller animals.<sup>5, 6</sup>

The degree of capillary damage depends to an extent upon the intensity of the burn.<sup>7</sup> A burn of the dog's foot by water at 67 degrees C. for 10 seconds is a threshold burn; it produces a slight, transient increase in lymph flow from that foot and a small but significant rise in concentration of the lymph protein. More intense burns, by hotter water and by longer immersion, are followed by greater flow and protein concentrations; but no matter how severe the burn,

the protein concentration of the lymph is never as high as that of plasma. A cooking burn of boiling water for 20 seconds resulted in a lymph protein concentration of only 5.0 Gm. while the plasma protein was 6.7 Gm. The findings in a typical experiment of the dog's foot with a burn of moderate severity are depicted in Chart 1; the protein concentration of the lymph rose after burning from 1.5 Gm. to 3.5 Gm./100 cc. (See also Table I; compare slight rise in protein concentration of lymph from left foot with that from more severely

TABLE I.—*Distribution of Albumin and Globulin Proteins in Arterial Plasma and Lymph from the Foot of Dogs Before and After Burning.*

Sample	Time Hours	Arterial Pressure mm. Hg.	Hema- tocrit % Cells	Protein Concentrations				NPN mg./100 cc.	
				Total Gm./100 cc.	Albumin Gm./100 cc.	Globulin Gm./100 cc.	AG Ratio		
Experiment No. 1									
Plasma	Pre-burn.....	..	131	44	5.9	4.4	1.5	3.0	23
	Post-burn.....	1	144	55	6.4	3.9	2.5	1.6	21
	Post-burn.....	2	...	62	6.1	3.7	2.4	1.5	22
	Post-burn.....	3½	143	68	5.9	3.5	2.4	1.5	31
Lymph	Pre-burn.....	...	...	..	0.9	0.7	0.2	3.5	31
	Post-burn.....	1	...	..	3.3	2.3	1.0	2.3	28
	Post-burn.....	3	...	..	4.1	...	...	...	27
	Post-burn.....	4	...	..	4.4	2.6	1.9	1.4	30
Experiment No. 2									
Plasma	Pre-burn.....	...	...	34	6.7	3.4	3.3	1.0	45
	Post-burn.....	4	...	32	6.6	3.4	3.2	1.0	83
Lymph	Pre-burn.....	...	...	..	2.2	1.1	1.1	1.0	..
	(Both feet)								
	Post-threshold burn	4	...	..	2.7	1.3	1.4	0.9	..
	(Left foot)								
	Post-severe burn...	2	...	..	4.5	2.9	1.6	1.8	..
	Post-severe burn...	4	...	..	4.5	2.6	1.9	1.4	..
	(Right foot)								

burned right foot.) It is thus clear that a portion only of the plasma protein passes with the water through the damaged capillary from blood vessel into the lymphatic; there is an unaccounted for fraction, 1.7 Gm. in the cooking burn described and more in less intense burns.

Where is this unaccounted for fraction of the protein? That it does not lodge in the wound is indicated by the observation that fluids removed by needle from the wound and exuding on the surface of the wound have protein concentrations slightly lower than that of the lymph.<sup>8</sup> There is only one place for it to be and that is still in the blood stream.

*Protein Concentration of the Residual Plasma.* If the unaccounted for plasma protein remains in the blood stream, dissolved in other plasma water, then the concentration of the protein in the residual circulating plasma must rise, not fall, immediately following the thermal injury. In support of this assumption is the finding of an increased protein concentration of the plasma

of dogs after burning. Plasma protein concentration was followed in 48 dogs burned experimentally (under nembutal anesthesia) and receiving no fluid therapy. In 38 an increase in the protein concentration was observed. In 23 of the 38, only one or two feet were burned and the protein elevation ranged from 0.1 to 1.3 Gm./100 cc., with an average of 0.44 Gm.; in three of these a subsequent dilution was noted, early in one (Experiment 1 of Table I) and late in two. In the other 15 a larger surface of four legs was burned and the protein concentration rose from 0.1 to 4.7 Gm., averaging a 2.09 Gm. rise. Of the 10 remaining animals of the 48, in six, no significant change in concentration was recorded, and in four, falls in concentration of 0.2, 0.3, 0.8 and 1.3 Gm./100 cc. were found. However, the first reading after the burning in each of the 10 animals was delayed, being respectively at the sixth, eighth, 28th and 19th hours in the four whose concentration fell. It is more than likely that a period of increased concentration was overlooked. (Of three dogs maintained under nembutal anesthesia but not burned, two showed a 0.2 Gm. decline and the third a 0.2 Gm. increase in the protein concentration; all three showed a slow rise in hematocrit.)

*Osmotic Tension of the Residual Plasma.* The increased concentration of protein found in the residual circulating plasma means an increase in the osmotic tension of the plasma which should be accompanied by a withdrawal of fluid from the unburned tissues of the body to the blood stream. The dilution of protein succeeding the initial increased concentration indicates such withdrawal (Experiment 1, Table I).

What evidence is there that the initially more concentrated plasma does not also take back water from the wound? The finding of the slightly lower protein concentration in wound and exudate fluid than in the lymph suggests resorption of water from the edema fluid before it enters the collecting lymphatic trunk. That such resorption by plasma of water in the wound is limited, however, is indicated by the following experiment, using hypertonic purified albumin.\* The lymphatic trunks of the hind feet, the neck and the thoracic duct were cannulated; a control flow of lymph was observed. The feet were then burned and when the typical curve of increasing lymph flow from the feet and rising serum protein concentration and hematocrit of the blood were established, the animal was given intravenously 31 Gm. of the albumin in a 25 per cent solution. The hematocrit fell promptly, reaching its lowest level two hours after the injection. This fall in hematocrit represented an enlargement of the plasma volume due to absorption of fluid from the tissues. That this fluid came virtually entirely from the unburned tissues and not from the burn wounds is indicated by cessation of the flow of the lymph from the cervical trunk and a drop in thoracic duct pressure while the increased flow from the feet engendered by the burn continued. There was a slight decrease in flow of the lymph from both feet in the first 20 minutes after the injection

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\* This experiment was carried out in collaboration with Dr. James T. Heyl. We are indebted to him for his help and to Professor Edwin J. Cohn for furnishing us with the purified bovine albumin used.

followed promptly by a secondary rise to a rate of flow as high as that before the injection. This transitory decline in flow was no greater than that often encountered in control experiments, but because it appeared simultaneously in both feet is believed to indicate a transitory drop in tissue pressure presumably due either to a decrease in rate of capillary filtration into the wound or to an increase in rate of water resorption from the wound area.

The cessation of flow of the lymph from the cervical region persisted for more than three hours in spite of massage and indicated severe dehydration of this unburned region of the body. The contrast between this cessation and the transitory decrease in lymph flow from the wounds suggests that the mechanism for resorption of water locally is also damaged by a burn, the only mechanism for return of fluid from the wound remaining intact being the lymphatic system.

The osmotic influence of the increased concentration of protein found in the circulating plasma (immediately after injury) upon the water concentration of the unburned tissues should depend in part upon its albumin globulin ratio. The lower the ratio the less dehydrating it should be. In the next section the differential permeability of the damaged capillary membrane to albumin and globulin and its effect upon the albumin globulin ratio of the residual plasma is, therefore, considered.

*Permeability of Capillary to Albumin and Globulin.* Perlmann, Glenn and Kaufman in 1943 examined by electrophoresis the serum and lymph of calves before and after burning.<sup>9</sup> In keeping with the earlier chemical analyses on dogs, as well as on calves, the serum proteins, albumin, alpha, beta and gamma globulins, are to be found in normal lymph; the relative amount of albumin in lymph is higher than in the serum. When first examined, two hours or longer following thermal injury in the calf, the albumin globulin ratio of both serum and lymph had fallen; a greater fall was encountered in the lymph from the burned than unburned leg. Perlmann *et al* concluded that a primary effect of the injury on the capillary wall was "the increased passage of the plasma proteins and a decrease in the differential permeability to albumin."

The permeability of the damaged capillary has been investigated in this laboratory with radioactive diazo dyes and by chemical analysis of the proteins in both the plasma and lymph of dogs. The experiments with the radioactive dyes have been published elsewhere.<sup>4</sup> The dyes, made radioactive by the chemical addition of radioactive bromine, have a rapid and preferential affinity for albumin.<sup>10\*</sup> When injected intravenously in less than saturating quantities they bind with the plasma albumin. The rate of their subsequent appearance in lymph is a measure of the rate of passage of albumin across the capillary membrane. Following a severe burn, immersion in boiling water for 60 seconds, the dye concentration in the lymph flowing from the burned foot

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\* The addition of two bromine atoms to the lipid soluble portion of the dye molecule apparently decreases water solubility; the colloidal property of the dye and its "fastness" as a dyestuff as well as its biologic properties relative to the protein bond are apparently unchanged.<sup>11</sup>

rose to that in the blood serum within less than an hour. The total protein concentration had risen in the lymph from 2.0 Gm. to only 4.3 Gm./100 cc. while in the serum it started at 7.1 Gm. and gradually rose to 7.7 Gm./100 cc. The conclusion from this experiment was that the capillary wall had become, as the result of the burn, wholly permeable to albumin but not to the globulins.

After a less severe burn, boiling water for only 15 seconds, the dye concentration took longer to rise in the lymph and never reached that of the serum, indicating a still incomplete though increased permeability to albumin.

The chemical analyses\*\* of the plasma and lymph proteins of dogs carried out in this laboratory support the concept of a predominant loss of albumin through the damaged as well as normal capillary membrane. The plasma proteins were examined in 11 experiments. In seven the albumin-globulin ratio fell, the minimum decrease being from 0.7 to 0.6 and the maximum from 1.5 to 0.6. These seven experiments include the three in which the ratio was measured at two hours or less after injury. Experiment 1 of Table I is one of these three; the pre-burn ratio was unusually high. In two experiments the ratio rose, from 1.0 before burning to 1.6 at the fifth hour and from 2.5 to 3.5 at the 28th hour, respectively, after burning. In the remaining two experiments the ratio did not change, including Experiment 2 of Table I in which the ratio was not measured within the first four hours after burning.

In only four of these 11 experiments was there sufficient lymph for chemical determination of the ratio both before and after burning. In two there was a rise in the ratio. This rise is illustrated in the lymph from the severely burned foot (right) of Experiment 2, Table I, the ratio being greater at two hours than four hours post-burn. There was no significant change in the ratio in this same experiment (Experiment 2, Table I) in the lymph from the lightly burned left foot; the total protein rose only 0.5 Gm. In the other two experiments, there was a fall in the ratio, but in both experiments the initial ratio of plasma and lymph was unusually high (see Experiment 1, Table I).

The fall of the albumin-globulin ratio of the plasma encountered immediately after injury should reduce the rise in osmotic tension indicated by the increase in concentration of the total protein.

*Abnormal Proteins.* Perlmann, Glenn and Kaufman in their electrophoretic studies in the calf discovered in the lymph from the burned leg a hitherto unseen protein in the range of globulin mobility. They conclude that the substance is a protein released from damaged cells. Our efforts toward identification of abnormal proteins were limited to a study of the activity of certain enzyme systems. Zamecnik<sup>13</sup> has been able to recover in the lymph from the burned feet of dogs specific peptidases of the types associated with intracellular enzyme systems; it is presumed, therefore, that they were released from the cells by the damage.

The amylase and cholinesterase activities of serum and lymph before and after burning have also been examined. The activities found in seven dogs,

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\*\* Chemical separation of the plasma and lymph proteins was carried out by the sodium sulfate method of Howe.<sup>12</sup>

both in serum and lymph, were proportional to the total protein concentrations. The slight variations in activity were no greater than those encountered in control animals. The variations usually, but not always, paralleled alterations in the protein concentration. These findings are interpreted to mean that there is no specific effect of burn trauma either upon the activity of the two enzyme systems as they relate to the extra-cellular fluid (plasma and interstitial fluid), or upon the permeability of the capillary membrane creating a predilection for their passage.

The fibrinogen level\* of blood and lymph was followed in four dogs before and after burning. The normal level of fibrinogen in the lymph was less than half that in the plasma. Following burning the level in both plasma and lymph rose, slightly in the plasma, more in the lymph until that of the lymph was approximately that of the plasma. (There was thus no evidence obtained in these few experiments of retention of fibrin in the wound.)

#### CLINICAL OBSERVATIONS

It has not been feasible to examine the lymph of burned patients; analysis of the changes in capillary permeability and the shift of protein to the wound, therefore, must depend upon a comparison of blood plasma and the fluid removed from the blebs of the wound.

The chemical and electrophoretic studies of plasma and bleb fluid carried out on this series of burned patients confirm those on animals. As the plasma circulating through the wound area loses water into the wound, a portion of the proteins dissolved in that water is retained within the vascular tree, and there is conse-

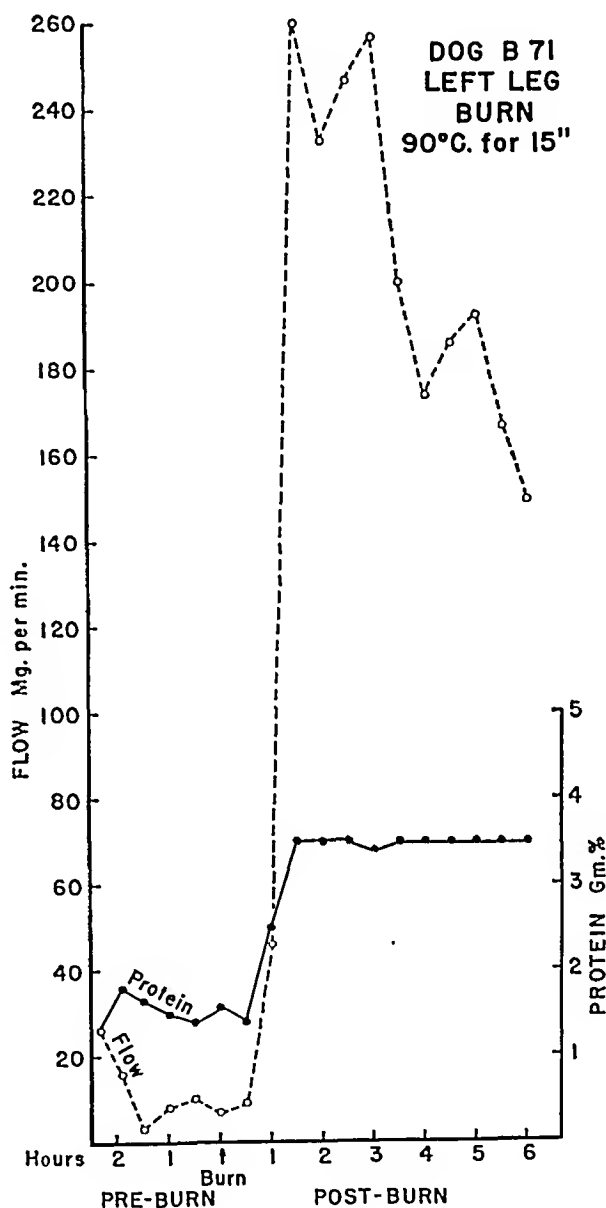


CHART I.—The increase in flow and protein concentration of lymph from the foot of a dog following burning. The flow of lymph before burning was obtained only with massage; following the burn there was a spontaneous flow the rate of which rose precipitously in the first hour and a half. In the same period the protein concentration more than doubled. After maximum edema had been reached the flow gradually decreased but the protein concentration remained at the same elevated level.

\* Fibrinogen of plasma and lymph was measured by the method of Cullen and Van Slyke.<sup>14</sup> The normal plasma level is from 0.3 to 0.6 Gm./100 cc.



quently an initial rise in plasma protein concentration and in osmotic power.

*Contrast of Plasma and Bleb Fluid Proteins.* The literature records several measurements of the protein withdrawn from the blebs of burned patients;<sup>15, 16</sup> the concentrations recorded are 60 to 80 per cent of that expected of the plasma. The interval between injury and withdrawal of the fluid and a simultaneous plasma protein measurement are usually not also recorded.

The total protein concentration of the fluid of a number of unruptured blebs was examined at varying intervals following injury. The fluid was withdrawn, without breaking the bleb, by sterile needle and syringe inserted at the side or base of the bleb. A few of the patients afforded a sufficient number of blebs for repeated taps. A fluid was discarded if the gross appearance of the wound suggested infection or if the fluid was cloudy on withdrawal. Most of the fluids

TABLE II.—Concentrations of Plasma and Bleb Fluid Proteins of Burned Patients at Varying Intervals Following Burning.

Case No.	Time Post-Burn	Bleb Fluid Proteins				Plasma Protein Gm./100 cc.
		Total Gm./100 cc.	Albumin Gm./100 cc.	Globulin Gm./100 cc.	AG Ratio	
116	2 hrs.	4.2	See Table III		1.71	7.2
63	2 hrs.	4.6				
58	3 hrs.	5.1	3.9	1.2	3.2	
114	36 hr.	3.1	...	...	...	5.7
120	51 hrs.	4.3				
120	54 hrs.	4.7	...	...	...	6.5
81	3 days	4.4	2.8	1.6	1.8	
80	5 days	4.9	2.9	2.0	1.5	
119	5 days	3.6	...	...	...	6.6
119	5 days	3.2	...	...	...	6.5
119	6 days	4.0	...	...	...	6.5
28	5 days	3.6	2.1	1.5	1.4	6.1
28	6 days	3.3	...	...	...	5.9
28	12 days	2.5				
17	6 days	2.2	...	...	...	8.1
38	7 days	1.5	...	...	...	5.4
19	7 days	1.8	...	...	...	7.0

were cultured to insure exclusion if bacterial inflammation were present. The concentration of the plasma was measured simultaneously in most instances. The rate of passage of sulfadiazine from blood stream to bleb fluid was measured in three patients at intervals after injury (2, 60 and 100 hours) in order to ascertain whether the intimacy of bleb fluid and blood plasma persisted.

The total protein concentration of the fluid removed from a bleb of a burn wound was found to be always lower than that of the patient's circulating blood plasma. The chemical analyses from representative patients with partial thickness burns are given in Table II. The analysis of the electrophoretic pattern of the fluid and plasma of one of two patients, generously examined for us by Dr. G. E. Perlmann, is given in Table III. The protein concentrations of bleb fluid and plasma of patients correspond closely to those of the lymph from the burned foot and plasma of dogs. The highest concentrations

in the bleb fluid are found within the first days following the burn. The fluids withdrawn after the fifth day show concentrations decreasing with time, suggesting not only resorption or breakdown of proteins as healing progresses, but also that the protein concentration of the normal interstitial fluid is considerably lower than that of the wound edema fluid, and at least as low as that of the normal peripheral lymph of the dog.

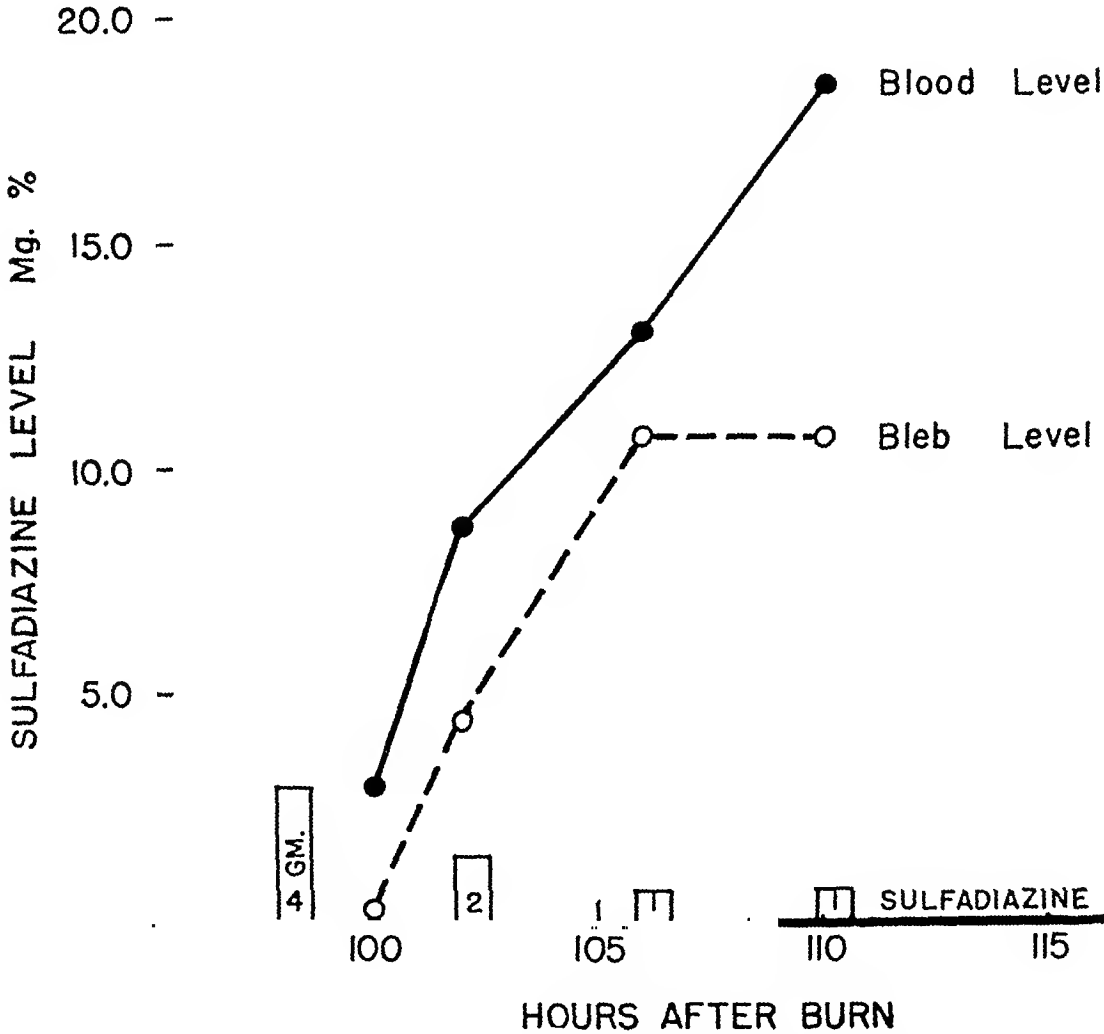


CHART II.—Case 119. Concentration of sulfadiazine in blood and bleb fluid after withholding the drug until the fourth day. The patient had a partial thickness skin burn with multiple blebs. Four grams of sulfadiazine were given by mouth 98 hours after the burn. The rise in concentration in the bleb fluid is almost as prompt as in the blood stream indicating rapid exchange through the wound even at this late time after the burn. (Reprinted with the permission of The Journal of the American Medical Association.)

The albumin-globulin ratio of bleb fluid is high, higher than that of the plasma in the first hours after injury (see Table II, Case 58, and Table III). The observations made after 36 hours show it to be in the range of that of normal plasma. Too few observations have been made to tell when the ratios of plasma and bleb fluid approach each other. The ratio of the one bleb fluid observed at 36 hours was still increased as compared with that of the plasma, but the plasma had an abnormally low ratio and total protein concentration, perhaps related to the patient's preexisting, diffuse osteoporotic disease of the bones of unknown etiology.

The results of the study of the passage of sulfadiazine from plasma to bleb fluid have already been reported<sup>17, 18</sup> but a resumé is given here to emphasize the rapidity with which the plasma and the fluid of the non-infected burn bleb communicate with each other, even as long as five days after injury. To a patient with several blebs suitable for multiple tapplings, sulfadiazine was given by mouth at the ninety-eighth hour after burning (Chart II). The level of sulfadiazine was observed in both plasma and bleb fluid by analysis of samples of each fluid taken at the second, fourth, eighth and twelfth hours after the first dose of sulfadiazine. The rise in the level of sulfadiazine in the bleb fluid was found to lag only slightly behind that in the plasma.

These observations in burned patients point to an increased but incomplete permeability to protein of the capillary membrane damaged by a burn, as in the dog. There is apparently a greater permeability to albumin immediately following injury. That the findings in the bleb fluid are not due to a stagnant puddling of the fluid is suggested by the promptness of the passage of the sulfadiazine from the plasma into the bleb.

TABLE III.—*Electrophoretic Observations on Blood Serum and Bleb Fluid of Case 116. (Electrophoresis carried out in Na-diethylbarbiturate buffer of pH 8.6 and ionic strength 0.1)*

Time Post-Burn	Protein Gm./100 cc.	AG Ratio	Albumin	Concentrations in Percent of Total Protein			
				Globulin			
				Alpha-1	Alpha-2	Beta	Gamma
Serum No. 1—2 hours....	7.2	1.00	50.0	7.9	6.4	18.9	16.5
Serum No. 2—6 hours....	5.5	.85	45.9	10.1	11.3	17.8	14.9
Bleb fluid—2 hours.....	4.2	1.71	63.1	7.4	3.7	12.3	13.5

*Protein Concentration of Residual Plasma.* If one can assume that bleb fluid is essentially burn wound fluid, the filtrate from the damaged capillaries, the finding that the bleb fluid protein concentration is lower than that of the plasma, indicates that only a part of the plasma protein escapes with the plasma water from the capillary into the wound.\* In the patient as in the experimental

\* In the burn wound both of the human being and of the dog there are doubtless gradations of capillary damage and of increased permeability of the capillary membrane. The capillaries nearest the surface must receive the maximum trauma and their membranes may be rendered so permeable that circulation ceases within them, the lumen becoming plugged with cells. Those deepest in the wound must receive minimal damage and, as judged by the experimental observations,<sup>7</sup> allow to seep out a fluid only slightly increased in volume and with a protein concentration only slightly higher than normal. From the capillaries between these extremes, the volume and the protein concentration of the filtrate presumably varies with the depth of the capillary. Thus the wound fluid, or the lymph flowing from a wound, should be a mixture of capillary filtrates. Whether or not the fluid is a mixture is an academic question; the concentration of protein remaining in the vascular tree will depend upon the final concentration in the entire wound area and the total volume of fluid seeping into the wound rather than upon the concentration of the filtrate from any one capillary.

# PLASMA PROTEIN SHIFT IN THERMAL TRAUMA

animal, therefore, an increase in concentration of the protein in the residual circulating plasma is to be expected in the first hours after injury. It is of course not possible to obtain in the burned patient the necessary control blood sample to test this assumption, for the patient arrives in the hospital already burned. Based on two sets of observations, we have the impression, however, that such is the case.

The protein concentration of the plasma within the first three hours after injury and before the onset of therapy in 19 extensively burned patients in whom this measurement was obtained, was 7.0 Gm./100 cc., the range being from 6.3 to 7.7 Gm. The lowest level encountered was in the plasma of a six-year-old boy who had long been a feeding problem and was undernourished; also included are another previously ill patient and three chronic alcoholics, all of whose levels were among the lowest found. The average of the highest protein concentration observed within the first 12 hours after injury and after onset of therapy in 46 patients with either extensive burns or circumscribed

TABLE IV.—*Plasma Protein Concentration of Two Extensively Burned Patients in the Initial Hours after Injury.*

Case No.	Extent of Burns	Hours After Burning	Plasma Protein Gm./100 cc.	Hematocrit % Cells
217	78%	0.8	6.9	50
		1.5	6.5	43
		5.5	6.9	50
		8.0	8.0	51
		11.0	7.3	48
		17.0	6.0	39
		20.0	5.4	42
254	45%	1.3	7.7	50
		3.5	8.0	50
		4.5	7.1	47
		8.0	7.4	46
		11.0	7.4	47
		14.5	6.4	43

skin burns and pulmonary damage, was 7.5 Gm./100 cc., with a range of 6.3 to 9.5 Gm. These averages and ranges are above those generally accepted as normal. Phillips, Van Slyke *et al*<sup>19</sup> give a range of 6.0 to 7.3 Gm./100 cc. Our own observations agree with this range for normal adult human beings.

The reinforcement of the concept that the initial change in plasma protein level is toward an increasing concentration was encountered in burned patients whose therapy was either delayed or adjudged inadequate in the first few hours after entry to the hospital. The findings in two patients (Cases 217 and 254) illustrating this event are given in Table IV. During the period of inadequate treatment there was either no change or a rise in the total protein concentration of the plasma. Inadequacy of therapy in these patients was judged by the failure of the hematocrit to fall promptly toward normal, or

because it rose further, or because the urinary output was meager. In contrast, the extensively burned patients receiving therapy adequate for rehydration as judged by a falling hematocrit and renal output of 30 cc. or more per hour, were found to show a decrease in plasma protein concentration.

#### COMMENT

Survival of the burned patient depends upon the maintenance of a physiologic environment for the cells of the unburned organs. Excessive dehydration or hydration can conceivably result in irreversible injury. From examining the shift in protein from capillary to wound, the character of the residual protein in the plasma has been determined; it is this protein which controls the osmotic balance between plasma and the interstitial fluids caring for the nutrition of the unburned cells. Its initial increase in concentration in the absence of therapy means that the unburned tissues are being dehydrated.

Two qualifications are indicated in interpreting the observations recorded in this paper. The osmotic tension of the residual circulating plasma is presumably not as high as suggested by the total protein concentration; the decrease in the albumin-globulin ratio tends to cancel the rise in osmotic power. No measurements of the osmotic tension were carried out.

The second qualification is in regard to the origin of the decrease in the albumin-globulin ratio in the plasma. In addition to the preferential loss of albumin through the damaged capillary into the wound, new globulin may be added to the circulating plasma. White and Dougherty<sup>20</sup> have described in experimental animals a disintegration of lymphocytes with release into the circulation of globulin protein as a result of the administration of either adrenotropic or adrenocortical extracts. Selye has found adrenotropic and adrenocortical hyperactivity to be an expected sequel of trauma.<sup>21</sup> The relation of the lymphocyte-protein release to the endocrine system in the human being following burn trauma is discussed in a subsequent paper.<sup>22</sup> But it remains to be discovered to what extent in the burned patient such a reaction to trauma contributes to the change in albumin-globulin ratio of the plasma of the burned patient. It obviously cannot account for the entire fall of the ratio in the plasma; in such case the ratio in the lymph of the burned dogs and in the bleb fluid of the patients would be identical with that of the plasma.

The seeming difference between the observations of Perlmann, Glenn and Kaufman in the burned calf and ours in the burned dog and human being is probably one of interpretation, not of fact. It is possible that had Perlmann et al measured samples of lymph within the first two hours after injury, results comparable to ours in the same period would have been found.

The interest of Perlmann and her colleagues was centered on the search for abnormal proteins, the result of burn damage; a hitherto unidentified protein in the range of globulin mobility was disclosed by electrophoresis in the burned calf. Doctor Perlmann was unable to find by electrophoresis a comparable protein in the bleb fluid or plasma of the two patients of this series examined by her. In examining the bleb fluid of nine of the burned and one

frostbitten patient, Doctor Zamecnik found 11-fold differences in peptidase activity indicating the occasional release of such intracellular enzymes in the wounds of human beings as well as in dogs. Our search for other abnormal proteins in burned patients by measurement of cholinesterase and amylase activity of bleb fluid and plasma proved negative.

#### CONCLUSIONS AND SUMMARY

The nature of the shift of protein from the vascular bed into the burn wound has been examined experimentally and in the burned patient. In the dog the flow of protein through the wound has been measured by collecting lymph and in the patient by comparison of plasma and bleb fluid. Comparable results with the same implications have been found in the dog and the human being.

Proteins and fluid are in continuous slow circulation through the burn wound, returning to the blood stream via the lymphatics. The free flow in the lymphatics apparently accounts for the rapid resorption of edema in the uninfected burn wound after 48 hours;<sup>23</sup> as the capillary membrane heals, resorption is more rapid than the filtration from capillary into wound.

The total protein concentration of fluid in the burn wound is always lower than that of the plasma; more water than protein is lost from capillary into wound. The initial change in the residual circulating plasma is therefore an increase in concentration of total protein. This more concentrated plasma presumably exerts an increased colloid osmotic pressure in the unburned regions of the body. Following resorption of water from unburned tissues and fluid therapy, this increased concentration of the proteins of the residual plasma is replaced by a dilution.

The initial increase in protein concentration and osmotic power of the circulating plasma is not encountered following a hemorrhage of whole blood where the entire plasma is lost.<sup>24</sup> For a given loss of water from the vascular bed, that is for an equal reduction in blood volume, the undamaged tissues of the burned patient face a more rapid dehydration than those of the patient following a hemorrhage.

In addition to differences in total protein concentration, there are also differences in the albumin-globulin ratio of wound fluid and plasma. These differences depend upon differential capillary permeability; a greater than normal proportion of albumin passes the damaged membrane. The wound fluid thus has a higher ratio than plasma and the plasma ratio falls initially. This fall in ratio of the plasma presumably tempers the rise in osmotic power indicated by the increase in total protein concentration.

In a search for abnormal protein as a result of the injury, enzyme systems have been investigated in both plasma and lymph. An increase in activity was found of a peptidase of intracellular type in dog lymph following burning with divergent activities in bleb fluid of the human being.<sup>13</sup> The amylase and cholinesterase systems of blood and lymph of the dog were also studied before

and after burning. Neither evidence of disturbance of these enzyme systems nor of preferential passage of these proteins through the damaged capillary membrane was found.

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# TRAUMATIC CHYLOTHORAX\*†

A REVIEW OF THE LITERATURE AND REPORT OF A CASE TREATED BY  
LIGATION OF THE THORACIC DUCT AND CISTERNA CHYLI

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## INTRODUCTION

TRAUMATIC CHYLOTHORAX, according to Zesas,<sup>77</sup> was first described by Longelot in 1663. It is a rare condition with a grave prognosis. In 1938 Shackelford and Fisher<sup>65</sup> reviewed the literature, discarded 11 incomplete cases, summarized 39 remaining, and added two of their own. In 1947 Lampson<sup>40</sup> summarized 17 subsequent reports and added one of his own, making a grand total of 59 which have been recorded. Olsen and Wilson<sup>53</sup> were able to find only nine cases of chylothorax from any cause in the records of the Mayo Clinic, but since seven of these nine were discovered between December, 1942, and November, 1943, they concluded that chylothorax is more frequent than a review of the literature might indicate, and that the diagnosis is frequently not made. On the other hand, Elliott and Henry<sup>24</sup> found only two cases out of a total of 600 samples of hemothorax fluid examined, covering an "experience of far more than a thousand chest wounds." The relative infrequency of chylothorax in war wounds is explained on the basis of the close proximity of the thoracic duct to vital structures, injury of the one implying fatal damage to the others.

## EMBRYOLOGY AND ANATOMY

Lymphatics arise independently of blood vessels from discrete mesenchymal spaces which become lined by endothelial cells. The adult lymph system is derived by a process of fusion and budding of these anlagen. Lymph sacs develop with openings into veins. Two of these, the right and left jugular, persist and become the openings of the right lymphatic duct and the thoracic duct, respectively, into the great veins of the neck. Another lymph sac, lying anterior to the body of the second lumbar vertebra, becomes the cisterna chyli. The embryonic thoracic ducts are bilateral and have numerous cross anastomoses. Persistence of these real or potential cross anastomoses becomes an important factor in the development of collateral lymph circulation following injury to or obstruction of the duct.<sup>41</sup>

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The anatomy of the thoracic duct has been investigated by numerous authors.<sup>10, 17, 55, 61, 69</sup> The duct varies from four to six millimeters in diameter. Its walls are composed of smooth muscle and fibrous tissue.<sup>1</sup> It has its origin from an irregular triangular sac-like dilatation, the cisterna chyli, which is situated on the anterior surface of the body of the second lumbar vertebra, to the right side of and behind the aorta, by the side of the right crus of the diaphragm. Tributary trunks, the bilateral lumbar and the intestinal, enter the cisterna from below. Immediately cephalad, at the commencement of the thoracic duct, on either side, is a descending trunk draining the lymph from the lower six or seven intercostal spaces.<sup>32</sup> Entering the thorax through the aortic hiatus of the diaphragm, the duct ascends between the azygos vein and the aorta to the fifth thoracic vertebra, where it inclines toward the left, enters the superior mediastinal cavity, and ascends behind the arch of the aorta and the left subclavian artery, and between the left side of the esophagus and the left pleura, to the upper orifice of the thorax. Passing into the neck the duct forms an arch which rises to a variable extent (as much as five and one-half centimeters)<sup>39</sup> above the clavicle. It then crosses anterior to the subclavian artery, the vertebral artery and vein, and the thyrocervical trunk or its branches, and empties into the vascular system at the angle of junction between the left subclavian and left internal jugular veins.

The right thoracic duct is about 1.25 centimeters long, and normally ends in the right subclavian vein at its junction with the right internal jugular. This duct and its tributaries drain the right side of the head and neck, the right upper extremity, the right side of the thorax, right lung, right side of the heart, and part of the convex surface of the liver.

Lymph from the remainder of the body, and intestinal chyle, pass into the venous system by way of the main thoracic duct.

The lower thoracic duct and cisterna chyli represent the "hub" or central collecting point of the chyle and the major portion of the lymph from the entire body.

The usual textbook description of the thoracic duct, as above portrayed, does not take into account the extreme variability, based on differences in embryonic development, which may occur.

Davis<sup>17</sup> described nine types, ranging from the complete persistence of bilaterally symmetrical ducts to the persistence of one single trunk. Stuart<sup>69</sup> summarized the anatomic variations of the thoracic duct and said that the usual description as a single channel throughout its course "may almost be regarded as a description of an abnormality, so frequently is it found to branch and subdivide." He mentioned cross anastomoses between double branching ducts within the thorax and called them "surgically unimportant"!

Brinton<sup>10</sup> described the various ways in which the thoracic duct empties into the veins of the neck. He stated that at the mouth of the duct in the wall of the vein there are two valves which prevent backflow of blood into the lymph channel. Sometimes it empties into the right side, and sometimes there are several openings into the vein, producing a delta-like arrangement.

Parsons and Sargent<sup>55</sup> showed that the duct has two terminal branches in 18 out of 40 cases.

Dissections at the Rhode Island Hospital, carried out by Dr. Charles Begg (Fig. 4), have emphasized the important relationship of the thoracic duct to the sympathetic nervous system. It is not generally recognized that low in the right chest the duct may lie directly against the azygos vein and that the great splanchnic nerve may lie directly over the vein. These relationships vary. Frequently the splanchnic nerve is within a few millimeters of the thoracic duct at this level.

Variations in position of the sympathetic nervous system likewise occur and in those subjects where the great splanchnic nerve enters the abdomen through the aortic hiatus<sup>57</sup> the thoracic duct and splanchnic nerves are of necessity very closely related.

Because of its many variations in position and its close proximity to the esophagus, pericardium, pleura, great vessels and sympathetic nerves, surgical injury of the thoracic duct has become an increasingly important hazard as modern surgery invades the deeper structures of the neck, chest and upper abdomen. Harvey Cushing's statement<sup>15</sup> is no longer true that the main part of the duct lies in a surgically forbidden region of the body and that "in the neck alone, and there only, under unusual circumstances is it accessible."

#### PHYSIOLOGY

The function of the thoracic duct is the conveyance of chyle and lymph into the general circulation. Chyle flows at the rate of .38–3.9 cubic centimeters per minute<sup>14</sup> or at the rate of 60–190 cubic centimeters per hour.<sup>42</sup> With complete severance of the duct it is therefore theoretically possible to lose over four liters within a 24-hour period. Pressure within the duct is normally low, but after ligation may be as high as 35 centimeters of water.<sup>23</sup> Flow of chyle is favored by the slightly higher pressure in the duct than in the veins and by respiratory motion with its fluctuating changes of intrathoracic pressure. Intestinal peristalsis, muscular activity, and coughing or straining increase the intraductal pressure. Beck<sup>5</sup> suggested that the pulsations of adjacent arteries may be an important factor in producing lymph pressure.

#### CHYLE

The composition of chyle is unique and characteristic<sup>30</sup> and has been described by many authors.<sup>20, 30, 44, 47, 51, 72</sup>

The chief characteristics of chylous fluid<sup>37</sup> are:

1. Milky appearance.
2. Generally shows distinct creamy layer on standing.
3. Finely emulsified, with fine fat globules.
4. No odor or odor corresponding to that of food eaten.
5. Alkaline reaction.
6. Specific gravity generally exceeds 1.012.
7. Degree of opalescence more or less constant.
8. Sterile and resists putrefaction.

9. Fat content generally high, 0.4 to 4 per cent, and like fat in food.
10. Total solids usually greater than 4 per cent.
11. Total protein generally exceeds 3 Gm. per 100 cubic centimeters.
12. Salts and organic substances approximate the values found for chyle from the thoracic duct.

The chemical analysis of chyle and lymph in man (Munk), quoted by Lewin<sup>44</sup> is as follows:

	<i>Chyle</i>	<i>Lymph</i>
Water	92.2 per cent	95.2 per cent
Solid	7.8 per cent	4.8 per cent
Fibrin	0.1 per cent	1.0 per cent
Proteins	3.2 per cent	3.5 per cent
Fats, licithin and cholesterin	3.3 per cent	traces
Extractives	0.4 per cent	0.4 per cent
Salt	0.8 per cent	0.8 per cent

Sixty to 70 per cent of ingested fat is conveyed to the blood stream by way of the thoracic duct.<sup>7</sup> The fat content of chyle varies with the diet.<sup>62</sup>

The protein content of chyle is less dependent on diet and varies from one to six Gm. per 100 cc.<sup>22</sup> It is usually above three Gm. per 100 cc.

Lampson<sup>40</sup> has demonstrated that chyle is bacteriostatic against cultures of *Escherichia coli* and *staphylococcus aureus*. His work explains the fact that chyle resists putrefaction. Empyema is rarely mentioned as a complication of chylothorax in the literature.

Chyle is an important vehicle for the mobilization of proteins. In the presence of hemorrhage, protein is redistributed via the thoracic duct and made available for essential functions.<sup>13</sup>

Any description of chylous fluid is incomplete without mention of the fact that it is rich in lymphocytes. Injuries to, or obstruction of the thoracic duct are known to be associated with diminution or disappearance of lymphocytes and eosinophiles from the circulating blood.<sup>6, 22, 51, 60, 66, 75</sup> Davis and Carlson<sup>16</sup> state that "normally the lymphocytes enter the blood with the lymph stream, and not by direct migration through the capillary walls from their place of formation. They are as much a part of the lymph as the erythrocytes and leucocytes are of the blood. Red blood cells are not to be regarded as normal constituents of the lymph."

A progressive fall in lymphocyte percentages in the blood is one of the clinical manifestations of chylothorax.

We have been unable to find any explanation for the reported reduction or disappearance of eosinophiles.

#### ETIOLOGY OF CHYLOTHORAX

The causes of traumatic chylothorax as described by Shackelford and Fisher<sup>65</sup> and Lampson<sup>40</sup> are shown in Table I.

It is possible that these summaries may not include all reported cases of traumatic chylothorax when it is remembered that so-called spontaneous

cases, especially in infants,<sup>9</sup> may actually have been produced by hyperextension of the spine during delivery, or too vigorous manual attempts at resuscitation<sup>25</sup> or coughing and vigorous crying.

It is interesting to note that no cases of surgical trauma of the thoracic duct were mentioned in Shackelford and Fisher's report and that four cases of surgical intrathoracic injury of the thoracic duct resulting in chylothorax have

TABLE I

	Shackelford and Fisher (1938)	Lampson (1947)
Crushing injuries.....	17	1
Wounds (bullet and stab).....	8	5
Fall from height.....	6	2
Blow on chest.....	5	2
Thrown against seat of auto.....	4	..
Hyperextension.....	1	..
Auto accident with collision.....	..	2
Hit by auto.....	..	1
Severe coughing.....	..	1
Surgical accident.....	..	4
	41	18

been reported since 1938. These resulted from lysis of adhesions of the left lung by thoracoscope,<sup>21</sup> resection of a Ewing's tumor of the right tenth rib and vertebra,<sup>66</sup> and from injury to the duct during sympathetic denervations.<sup>50, 75</sup> The first two survived; the last two died.

In Whitcomb and Scoville's case injury to the duct was recognized at the time of sympathectomy and the duct was doubly occluded, above and below, with silver clips. The patient nevertheless developed chylothorax and subsequently succumbed during the intravenous administration of chyle. It occurs to us that metal clips are not the safest agents available for the ligation of such a delicate structure as the thoracic duct.

Peet and Campbell's case likewise occurred as a complication of sympathectomy and succumbed suddenly following surgical ligation and the intravenous administration of chyle.

Although only four cases of accidental intrathoracic surgical injury of the thoracic duct resulting in chylothorax have been reported, such injuries are not as rare as might be supposed.

We know of one recent case of traumatic chylothorax following sympathectomy<sup>67</sup> and another as a result of erosion of the thoracic duct from a catheter placed in the chest for drainage of an empyema.<sup>12</sup> Several cases have been observed following resections of the esophagus<sup>12, 70</sup> for tumors of that organ.

Occasional injury of the thoracic duct is inevitable, even in the most experienced hands, during extensive intrathoracic procedures, especially esophagectomy and sympathectomy. Indeed, the adequate removal of certain tumors of the esophagus may require deliberate section of the duct. Smith-

wick<sup>67</sup> estimates that he has injured the thoracic duct 15 or 20 times in his extensive experience with thoracolumbar sympathectomy. Chylothorax developed in only one case, where injury of the duct at the time of operation was not recognized and adequately treated.

The importance of recognition and immediate appropriate treatment of accidental surgical injuries of the duct in the prevention of chylothorax cannot be overemphasized.

#### PATHOLOGY

There is considerable discussion in the literature as to the actual mechanism of the development of chylothorax following injury to the thoracic duct, since anatomically the duct is extra-pleural in position, and since chylothorax, by definition, is an accumulation of chyle within the pleural cavity. Watts<sup>74</sup> quoted Hammesfahr to the effect that chyle escapes into the pleural cavity through the normal intercellular spaces between the endothelial cells, but Lillie and Fox<sup>15</sup> quoted J. L. Yates to the effect that there are no intercellular spaces in this region, and a perforation of the pleura is always present though frequently not recognized.

Blalock, Cunningham and Robinson<sup>6</sup> state that in their experimental animals "chyle entered the pleural cavity through an uninjured pleural layer."

Retropleural accumulations of chyle have been reported,<sup>11, 17, 51</sup> and it is probable that the usual delay which occurs between injury and the development of chylothorax represents the time required for erosion of the contiguous pleura and perforation of an enlarging chyloma into the pleural cavity.<sup>53, 65</sup>

#### DIAGNOSIS

Traumatic chylothorax is more common on the right than on the left except in the case of penetrating injuries, where it is more common on the left.<sup>47, 74</sup> As a general rule, injuries low in the thorax result in right chylothorax and high injuries in left.<sup>65</sup>

The signs and symptoms are what might be expected upon the rapid accumulation of chyle within the pleural cavity. The immediate effects are mechanical in nature, resulting from compression of the lung, reduction in vital capacity and perhaps a shift of the mediastinum, with angulation of the great blood vessels.<sup>65, 68</sup> They are as follows:

1. Delay in onset, two days to six and one-half years<sup>4</sup> following injury. The usual period of delay is two to ten days.<sup>75</sup>
2. Dyspnea—of sudden onset.
3. Shock, with elevated thready pulse, low blood pressure, pallor, cold clammy skin, and subnormal temperature.
4. Rapid and complete relief of symptoms following thoracentesis.
5. Reaccumulation of fluid and recurrence of symptoms, depending upon the quantitative escape of chyle into the pleural cavity.

The rapidity of onset and severity of symptoms, and the equally rapid relief following thoracentesis are characteristic and distinguish the condition from shock due to hemorrhage or other cause. Because of the pinkish gray

purulent appearance of the fluid, the unwary observer may be led into the mistaken diagnosis of empyema,<sup>19, 24, 74</sup> or hemothorax.<sup>45</sup>

The secondary symptoms and frequent lethal termination of chylothorax result from persistent loss of fluid, fat, protein and lymphocytes in cases where healing does not take place spontaneously or where successful surgery is not accomplished. In other words, the patient "bleeds" to death, his death being due to loss of lymph and chyle, rather than to loss of actual blood.

These signs and symptoms may be listed as follows:

1. Gradual or rapid loss of weight.
2. Dehydration.
3. Reduction in serum protein, mirroring a more significant loss of total body protein.
4. Reduction in blood and tissue fat.
5. Disappearance of lymphocytes and eosinophiles from the circulating blood.
6. Inanition, oliguria, thirst.
7. Death.

The patient may live for weeks or months, or die in a few days, depending upon the extent of the injury to the duct, complications of the original trauma, and the type and effectiveness of the treatment instituted.

Chylopericardium<sup>76</sup> and chylous ascites<sup>36, 46</sup> may occur in association with chylothorax. These are unusual and rare complications.

The diagnosis of chylothorax is not difficult. The clinical characteristics as described might conceivably be confused on rare occasions, but aspiration and laboratory identification of the intrapleural chyle gives conclusive evidence.

#### MORTALITY

Mortality rates for chylothorax approximate 50 per cent. In Mouchet's<sup>50</sup> 43 cases, the death rate was 41 per cent. McNab and Scarlett<sup>47</sup> reported 53 per cent and Lampson<sup>40</sup> 45 per cent out of a total of 58 cases analyzed.

#### TREATMENT

There is one universally stated and generally accepted maxim concerning the treatment of chylothorax to be found in the literature, and that is, "Do not operate." As has already been mentioned, Harvey Cushing described the intrathoracic duct as lying in surgically forbidden territory. In a personal communication to Lillie and Fox<sup>45</sup> in 1934, J. L. Yates said, "Ligation in the chest is almost certainly fatal." Florer and Ochsner<sup>27</sup> say, "Direct surgery to repair the duct has been completely unsuccessful, resulting in 100 per cent mortality." Following a practice attempt at ligation below the diaphragm in a cadaver Shackelford and Fisher<sup>65</sup> say, "Surgical ligation of the duct is physiologically compatible with life, but clinically impractical at present." The preponderance of opinion against direct attack upon the ruptured intrathoracic duct is almost overwhelming.<sup>3, 24, 25, 31, 66, 68, 74, 75</sup>

The accepted treatment of chylothorax has as its aim (1) Reduction of the volume of chyle and the prevention of respiratory and vascular collapse

from intrapleural pressure; (2) Maintenance of nutrition, and (3) Measures designed to favor healing of the injured duct. A summary of these various procedures follows:

1. Prevention of the mechanical effects of chylothorax.
  - a. Limitation of fluid intake.
  - b. Low fat diet.
  - c. Avoidance of lymphagogues, especially intravenously.<sup>5</sup>
  - d. Repeated thoracentesis.
2. Maintenance of nutrition.
  - a. High carbohydrate, high protein diet.
  - b. Maintenance of fluid balance.
  - c. Transfusions of blood, plasma, and blood substitutes.
  - d. Feeding of chyle by mouth.<sup>36</sup>
  - e. Feeding of chyle by rectum.<sup>34</sup>
  - f. Intravenous administration of chyle.<sup>3, 46, 52</sup>
  - g. Intrasternal administration of chyle.<sup>56</sup>
3. Measures to promote healing.
  - a. Phrenicotomy or phrenic neurotripsey.<sup>27, 51, 64</sup>
  - b. Pneumothorax.
  - c. Phrenicolysis and pneumoperitoneum.<sup>27</sup>
  - d. Retropleural drainage.<sup>11, 47, 63</sup>
  - e. Thoracotomy or thoracoplasty.<sup>58, 77</sup>
  - f. Injections of sterile broth.<sup>59, 64</sup>
  - g. Injections of Gomenol in oil.<sup>49</sup>
  - h. Intrapleural irrigations with azochloranid.<sup>31</sup>
  - i. Roentgen-ray therapy.<sup>53, 71</sup>
  - j. Surgical ligation.

One need only remember the mortality statistics of chylothorax to realize that the above measures are not eminently successful. Repeated thoracentesis and the maintenance of nutrition are certainly essential, but the latter is most difficult to achieve. In the last analysis, cure of the condition depends upon the establishment of collateral lymph circulation and/or the closure of the injured duct.

In cases of frank laceration of the thoracic duct, it is impossible to maintain normal fluid, fat, and protein reserves by dietary methods.<sup>46</sup> In spite of high protein diet, values for serum protein progressively decline. Limitations of fluid intake and dietary fat do not reduce the volume of chyle.<sup>62</sup> The progressive loss of protein is more important than is the loss of fat.<sup>48</sup>

Parenteral introduction of chyle, first recommended by Oeken,<sup>52</sup> has apparently been of benefit in some cases,<sup>3, 28, 64, 66</sup> but has not reduced the over-all mortality of 50 per cent.<sup>75</sup> This treatment is hazardous. Blalock and co-workers<sup>46</sup> reported the extension of a preexisting thrombophlebitis in their case following the administration of aspirated chyle. Schnug and Ransohoff<sup>64</sup> reported a marked phlebothrombosis which made intravenous administration difficult. In 1938 Johnson and Freeman<sup>38</sup> presented evidence that there is some hemolytic agent in chyle and in 1940 they<sup>29</sup> stated that only thoracic duct lymph has this property, other lymph not being hemolytic. In 1942 Whitcomb



and Scoville<sup>55</sup> reported a sudden death during the intravenous administration of chyle. They attributed the death to anaphylaxis. Other cases of sudden death following this treatment have been recorded.<sup>56</sup>

Phrenic neurotripsty, as recommended by Nowak and Barton,<sup>51</sup> is an ingenious suggestion, the object being to favor healing in low injuries of the duct. Healing in their case was "presumably due to elongation and narrowing of the crural sulcus with apposition of the diaphragmatic and mediastinal parietal pleurae." Other mechanisms suggested were reduction of the aspirating action of respiratory movements on the open duct and increased tendency for clot formation due to limitation of respiratory movements. The value of this treatment would depend in part upon the location of the lesion. It has been employed with doubtful results by several authors.<sup>27, 64</sup>

Other methods of indirect attack upon the injured duct are also of questionable value. There is no successful method of producing intrapleural tamponade by air or fluid.<sup>68</sup> Thoracotomy or thoracoplasty should be discarded. The injection of fibrinogenic agents is a blind and uncertain procedure. So far as drainage of retropleural chylomas is concerned, it would seem more logical to attack the duct directly, since the surgical exposure would be much the same. Roentgen-ray therapy might be of value if rupture of the duct were due to neoplasm.<sup>52, 53</sup>

#### INTRATHORACIC SURGICAL LIGATION OF THE THORACIC DUCT

We have been able to find only two recorded reports of surgical ligation of the thoracic duct in the chest for the treatment of chylothorax. The first of these<sup>56</sup> followed sympathectomy for hypertension. The patient was operated and the injured duct successfully ligated, but the patient died suddenly on the table. Chyle had been administered intrasternally without evidence of harmful effect in the preoperative period. Intravenous chyle was administered during the operation. Autopsy did not reveal the cause of sudden death.

Lampson<sup>40</sup> reported the second case. The cause of chylothorax in his patient was obscure, and was presumed to have been the result of strenuous coughing. His approach was through the left sixth rib bed. The duct was identified and ligated after incision of the mediastinal pleura anterior to the aorta, retraction of the esophagus anteriorly and the aorta to the left and posteriorly. One year following operation there has been no reaccumulation of chyle but his patient has great difficulty in maintaining her weight and there has been some residual fixation of the left chest.

Lampson mentions another case of successful ligation of the thoracic duct in the left chest by Dr. R. H. Meade, who approached the duct from behind the aorta, rather than from between the esophagus and the aorta. Lampson does not desire to report Meade's case, and does not include it in his historical review.

#### CASE REPORT—RHODE ISLAND HOSPITAL NO. 420265

Mrs. G. H., a 35-year-old housewife, was first admitted to the Rhode Island Hospital on December 10, 1941, complaining of headache of 2 years' duration. She was said to

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have had high blood pressure since the birth of the last of her 3 children 12 years previously. Her father and mother had been hypertensive.

Physical examination revealed marked elevation of blood pressure and rather extreme obesity (181 pounds). Preoperative sedation and other tests indicated a possible favorable outcome from sympathectomy, which was performed by one of us (R. R. B.) in two stages, on December 19th, and December 29th, 1941. Subcostal incisions, with removal of the twelfth ribs, were made. The diaphragm was incised, and the sympathetic chain removed bilaterally from the tenth thoracic to the second lumbar ganglion. As much of the distal splanchnic nerves as could be secured through the small diaphrag-



FIG. 1.—Chest X-ray taken before first paracentesis, demonstrating right chylothorax.

matic incisions used at that time were excised. The thoracolumbar nerve chains removed measured 12 centimeters in length and the splanchnics 8 centimeters. Renal biopsy revealed "no significant abnormality."

The patient was discharged much improved, with a satisfactory fall in blood pressure at rest, orthostatic hypotension, and complete relief of headache.

She was again admitted to the hospital 6 years later, on April 25th, 1947, complaining of increasingly severe headaches of 6 months duration. Her hypertension had recurred during the intervening years.

Physical examination demonstrated early retinal sclerosis (Grade II), moderate left ventricular hypertrophy and excellent renal function. Her weight was 180 pounds.

Sedation and other tests were again favorable and the patient was advised to accept extensive bilateral thoracic sympathectomy in two stages.

*Second Operation.*—On May 1st, 1947, a long vertical dorsolumbar incision was made on the right side, with the resection of two inches of the tenth and eleventh ribs near the spine. The posterolateral attachments of the diaphragm were incised down through the right crus and a wide exposure of the lower chest and upper retroperitoneal area made. Dense adhesions existed between the pleura and the diaphragm from the previous operation. There was no evidence of nerve regeneration except for a large neuroma of the great splanchnic nerve at about the level of the tenth rib. The thoracic chain and splanchnic nerves were removed to the mid-chest region, a biopsy was taken from the kidney, and the diaphragm and operative incisions closed.

Following operation the patient did so well that she was discharged on the eighth day, at her own request, with the understanding that she would return at a later date for sympathetic surgery on the left side. On the day of her discharge she walked easily,

TABLE II.—*Volume of chyle 32,180 cc. in 35 days. Accumulation of chyle began 10 days following injury of duct and ceased abruptly following ligation. Average protein concentration of the chyle was 3% and average concentration of lipids was 2.4%.*

RECORD OF CHYLE LOSS	
Days Post-Operative	Chyle Loss cc.
10.....	2,000
12.....	2,400
14.....	2,600
17.....	1,600
20.....	2,200
23.....	1,700
24.....	1,800
27.....	1,600
29.....	2,300
32.....	2,100
34.....	1,200
36.....	1,600
39.....	1,800
40.....	2,200
42.....	2,100
44.....	1,480
45.....	1,500
Total.....	32,180

without dyspnea. Her resting blood pressure was 145 millimeters of mercury systolic and 90 diastolic. Her breath sounds were reported as clear.

*Third Admission.*—Two days following discharge and ten days following sympathectomy the patient was returned to the hospital in a condition of collapse. She was cold, clammy and cyanotic. Breathing was rapid and labored. Her pulse was thready and elevated. Blood pressure in millimeters of mercury was 100 systolic and 80 diastolic and temperature was 98.0 degrees Fahrenheit. Immediate chest roentgenogram (Fig. 1) verified the clinical impression of fluid on the right side, and aspiration yielded 2000 cubic centimeters of pinkish-white fluid having the appearance and consistency of melted strawberry ice cream. Laboratory examination verified our impression that this fluid was chyle, not pus.

Clinical improvement following the first and many subsequent chest taps was dramatic. Respiratory and vascular collapse occurred once or twice each 48 hours, and before long the patient found herself requesting thoracentesis for relief of her symptoms.

The subsequent treatment and study of this patient was very difficult. Because of adiposity and thrombosis from her previous intravenous treatments, she had few accessible peripheral veins, and we were forced to rely for nutrition upon dietary measures alone. High caloric, high protein food, reinforced with casec egg-nogs, were employed but in spite of heroic efforts on the part of the staff and the patient her course was progressively downhill. Table II demonstrates that a total of 32,180 cc. of chyle was removed from May 10th to June 14th with a serious daily loss of fluid, fat and protein. There were 17 chest taps. In spite of the high carbohydrate high protein diet her blood serum protein fell from 7 Gm.% to 4.2 Gm.% (Fig. 2), lymphocytes practically disappeared from her circulating blood (Fig. 3), and her weight fell from 182 to 168 pounds. Phrenic neurotomy was performed under local anaesthesia on June 3rd, without benefit.

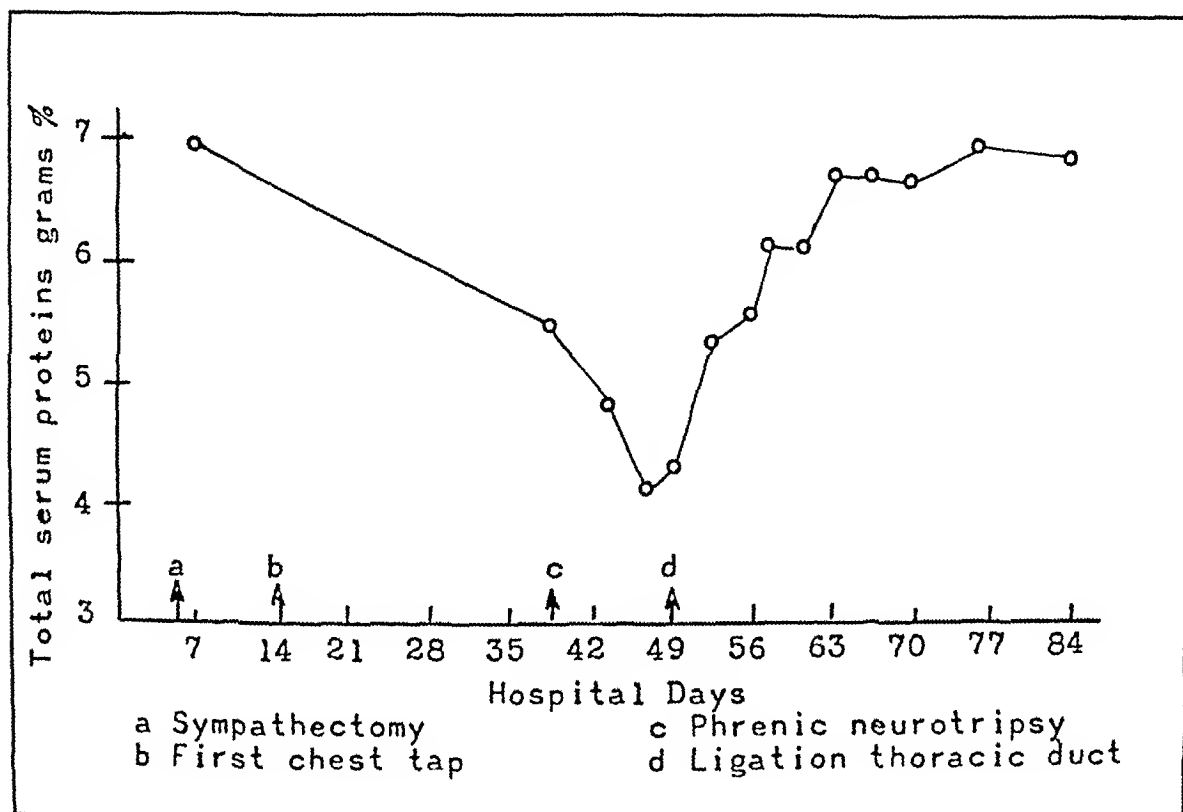


FIG. 2.—*The Course of Serum Protein Concentration.* During the phase of chylothorax an average of 919 cubic centimeters of chyle containing 28 Gm. (3 Gm.%) of protein were lost daily. Under these conditions, the serum protein concentration fell progressively and was not influenced by high protein diet or phrenic neurotomy. Dramatic and prompt elevation in the protein concentration occurred with ligation of the thoracic duct.

Intravenous amigen, blood plasma and whole blood were finally administered and the patient was reoperated on June 14th, 1947. Eight ounces of heavy cream were given by mouth four hours before surgery.

*Operation—June 14th, 1947.*—The chest was entered on the right side after resection of the 8th rib. Fifteen hundred cubic centimeters of chyle were aspirated. After some search, a sinus from which chylous fluid could be seen flowing was discovered leading down through the crus of the right diaphragm.

The mediastinal and diaphragmatic pleurae were incised and the diaphragm sectioned along its posterolateral attachments. The upper abdominal aorta was gently retracted and the cisterna chyli exposed with surprising ease. The draining sinus was readily followed to this structure, where a semicircular rent about one millimeter long was discovered on its anterior surface (Fig. 4). It would have been technically feasible to

have sutured this opening, or to have occluded the rent with fibrin foam soaked in thrombin solution, a technic which has subsequently been employed by Smithwick.<sup>67</sup> We decided to run no risks of recurrence of chylothorax. Ligation of the intestinal and lumbar branches would not have prevented back flow from the descending thoracic trunks or from the main duct, all of which were clearly visible. We therefore ligated the lower thoracic duct, the bilateral descending thoracic, the bilateral lumbar, and the intestinal trunks. Additional security for the closure was provided by suturing a flap of mediastinal pleura and a strip of oxycel over the rent in the cisterna. The diaphragm and operative incisions were closed without drainage. Silk technic was used throughout.

The postoperative course of this patient was essentially uneventful. Small amounts of serous fluid were aspirated on two occasions from the anterior lower right chest, but there was no recurrence of her chylothorax (Fig. 5). Mild transitory edema of the lower extremities, no more than might have been accounted for on the basis of hypopro-

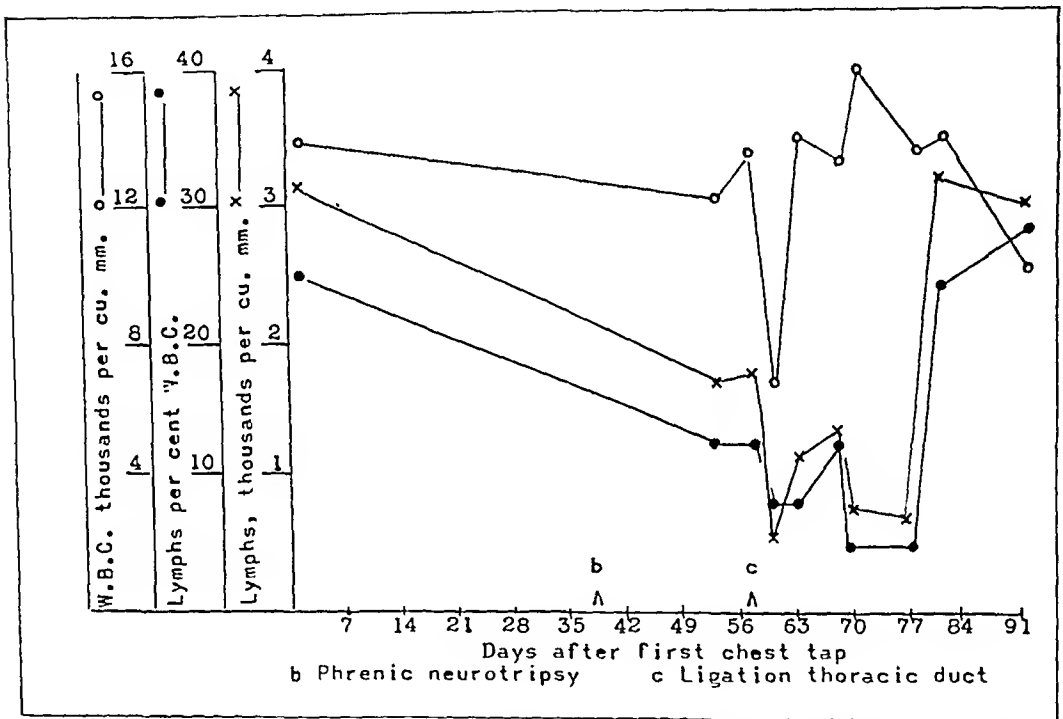


FIG. 3.—*A Demonstration of the Progressive Reduction of the Number of Lymphocytes.* The percentage of lymphocytes fell from 23 to 5 and the absolute number per cubic millimeter from 3151 to 675. The lymphocyte count was not influenced by phrenic neurotroipsy, but, after a brief delay, responded to thoracic duct ligation.

teinemia, was noted during the first postoperative week. There was no clinical evidence of ascites at any time, either before or following operation and no enlargement of the peripheral lymph glands or the spleen. Figure 6 demonstrates cessation of chylothorax, satisfactory and rapid return of serum protein values and lymphocyte percentages to normal, and a slight but delayed gain in weight following ligation.

Studies of the percentage of eosinophiles in the peripheral blood demonstrated a fall from 4 per cent at onset of chylothorax to almost complete absence (1 per cent or none on several occasions). This reduction persisted after a return of the lymphocytes to normal levels.

The patient was discharged from the hospital on July 4th, 1947, twenty days following

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ligation of the lower thoracic duct and obliteration of the cisterna chyli and its afferent trunks.

At the present time, six months following her last operation, she is in excellent health, free of headaches, and without evidence of fluid in her chest or abdomen. There is no peripheral edema. Her white blood count is normal; lymphocytes 22 per cent and eosinophiles 3 per cent. She is "dieting" and weighs 170 pounds.

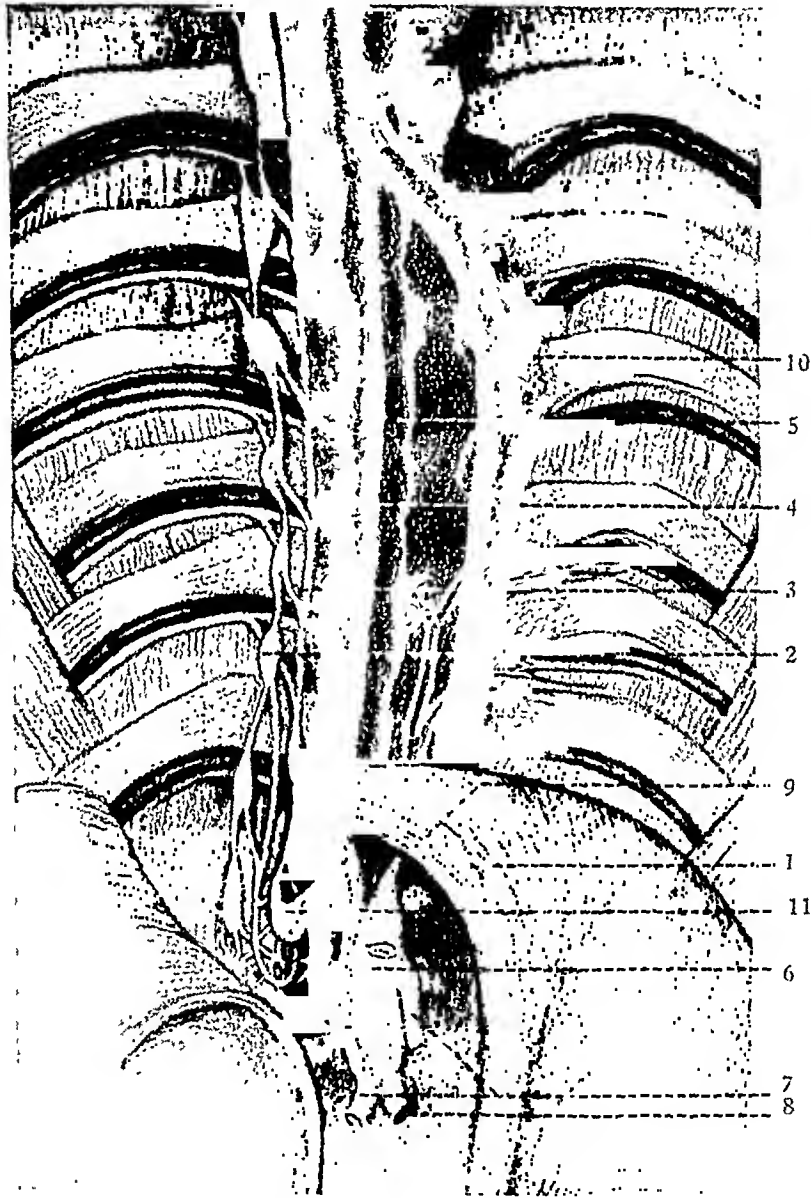


FIG. 4.—Artist's sketch demonstrating the relationships of the sympathetic nervous system in the lower right chest with the azygos vein and the thoracic duct. The cisterna chyli, with its bilateral lumbar and intestinal trunks are shown. The descending thoracic trunk on the left side, and the point of laceration in the cisterna are likewise demonstrated.

- |                               |                              |
|-------------------------------|------------------------------|
| 1. Diaphragm                  | 6. Cisterna chyli            |
| 2. Thoracic sympathetic chain | 7. Lumbar trunks             |
| 3. Splanchnic nerve           | 8. Intestinal trunk          |
| 4. Azygos vein                | 9. Descending thoracic trunk |
| 5. Thoracic duct              | 10. Hemi-azygos vein         |
|                               | 11. Celiac ganglion          |

## DISCUSSION

In view of the present prevailing high mortality of traumatic chylothorax and the numerous treatments recommended, the unfortunate surgeon who bears responsibility for such a case may be naturally uncertain concerning his proper course of action. Assuming that conservative measures fail, what is his justification for surgical attack? If the thoracic duct be ligated, by what route does chyle and lymph find its way into the general circulation? Is ligation physiologically safe and technically feasible?



FIG. 5.—Chest X-ray taken July 10, 1947; three weeks following ligation. The pleura is thickened, but there is no recurrence of chylothorax.

It has been abundantly demonstrated, both clinically and experimentally, that the integrity of the thoracic duct is not essential to life. Numerous cases of occlusions of the duct or of the receptaculum chyli due to carcinoma, tuberculosis, cyst or fibroma, without the development of chylothorax or chylous ascites have been reported.<sup>76</sup> It is probable that when chylothorax does develop under these circumstances, it is due more to erosion and leakage from the duct, or to interference with drainage by way of collateral branches than to actual obstruction.<sup>26</sup>

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Treatment of injuries of the thoracic duct in the neck has been discussed by numerous authors.<sup>8, 18, 35, 39, 50, 77</sup> Repair by suture or reimplantation into a vein has been advocated by some, but many successful cases of occlusion of the injured area by tamponade or ligature have been reported. In 1907 DeForest<sup>18</sup> said that a wounded thoracic duct should be treated exactly as a bleeding blood vessel,—by ligature, and Warschauer<sup>73</sup> even suggested the

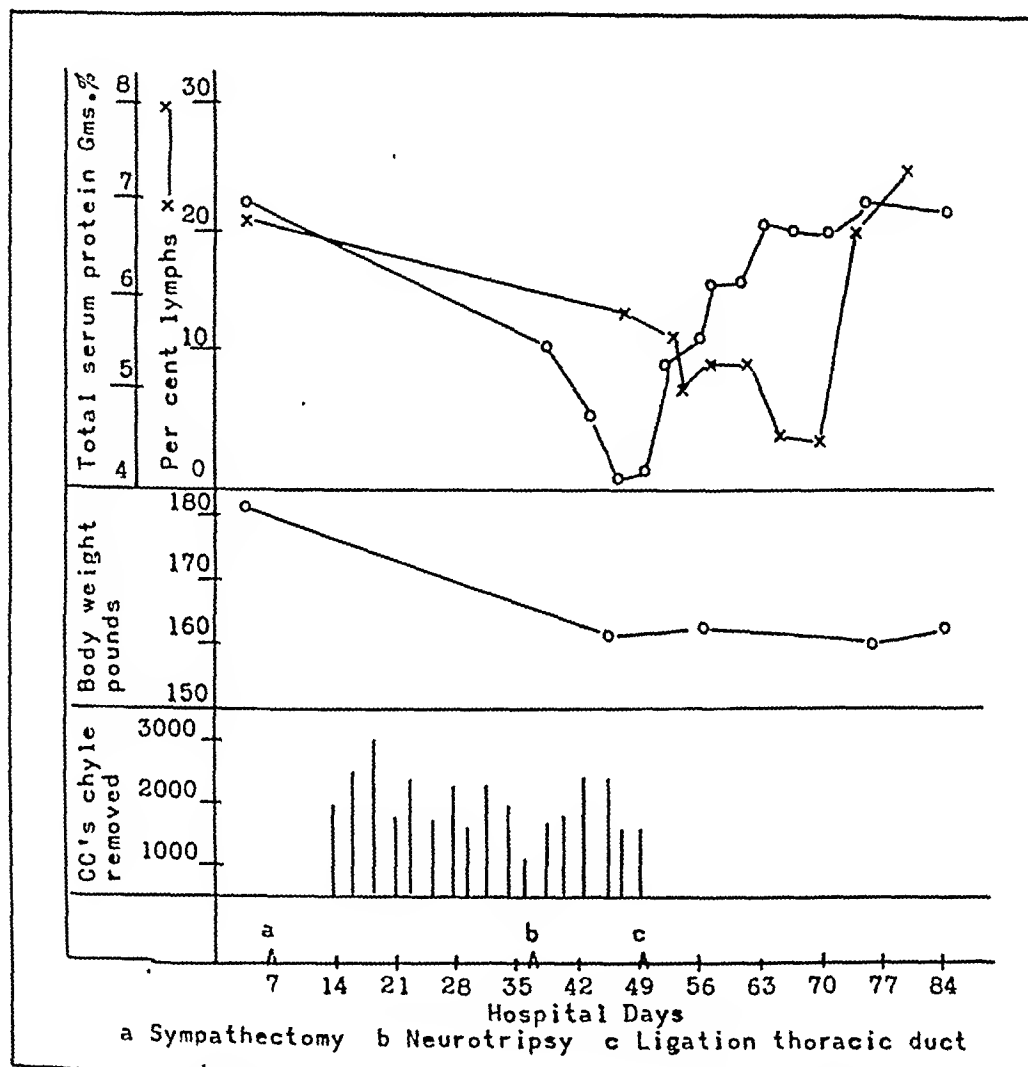


FIG. 6.—A Demonstration of the Effect of Chyle Loss on Body Weight, Serum Protein Concentration and the Number of Circulating Lymphocytes. The effects were not influenced by diet or phrenic neurotrippsy. The response to thoracic duct ligation was a prompt elevation of the serum protein concentration, arrest of body weight loss and a gradual return to normal of lymphocyte percentage in the peripheral blood.

advisability of intentional ligation of the duct in all operations in the neck where it might be endangered.

In spite of the relatively high pressure developed within the duct following ligation there is extensive experimental<sup>6, 13, 41, 43, 46, 50, 63</sup> and clinical evidence<sup>12, 15, 40, 54, 70</sup> that rupture of the duct or of the cisterna chyli does not occur.

One of us (R. R. B.) has witnessed ligation of the duct on several occasions where it had been injured in the supraclavicular triangle of the neck during the removal of malignant glandular metastases. In no case has there



been any postoperative evidence of chylous accumulations or of metabolic disturbances.

To Lee<sup>41</sup> goes the credit for the most thorough and convincing elucidation of this matter. After a review of the literature he described experiments in which he was able to demonstrate absolute intrathoracic ligation of the thoracic duct in experimental animals for the first time. None developed chylous effusions. The animals were sacrificed at variable intervals and autopsies performed. "As a result of these dissections, two general types of collateral circulation were established. The one type consisted of a collateral circulation to the right thoracic duct;—the other type comprised those cases in which lymph entered the azygos vein or its branches."

Lee described edema about the large lymphatic trunks and cisterna chyli following ligation, hypertrophy of the intra-abdominal lymph glands, and contraction of the duct above the point of ligature. By injection methods he demonstrated lymphatico-venous anastomoses between the cisterna chyli and the azygos, left intercostal, and left lumbar veins. Retrograde injections demonstrated possible channels as far as the hilum of the kidney and the subserous coats of the intestine. Lee concluded that non-functioning embryonic anastomoses exist between lymphatic and venous systems, and that these channels are capable of enlarging and functioning after ligation of the thoracic duct.

That ligation of the thoracic duct does not produce chylothorax has been demonstrated by others.<sup>6, 50</sup> Yater<sup>76</sup> concluded that,—“Many cases of obstruction of the thoracic duct are not associated with the accumulation of chylous fluid because of the normal collaterals which empty into veins.”

Blalock and co-workers,<sup>6, 60</sup> unable to produce chylothorax by ligation of the thoracic duct, found that this condition did develop in approximately one-half of their animals in which the superior vena cava had been occluded. If the death of these animals was prevented by repeated aspirations of chyle, frequently the lymph vessels would enlarge with the passage of time and the chyle would be returned to the venous system. They believe that there are lymphatico-venous communications in the peritoneal cavity..

On the basis of these considerations, when the patient with an injured thoracic duct presents a progressive downhill course, and conservative measures are failing, surgical ligation of the thoracic duct would appear to be a logical procedure.

Speculation as to how the cisterna chyli was injured in our case is fruitless. It was probably torn during the separation of retroperitoneal adhesions which had formed following the operation in 1941. From the clinical findings, we expected to find intrathoracic injury of the duct, not subdiaphragmatic injury of the cisterna. The recent operative suture line in the diaphragm probably provided a convenient point of perforation into the chest and explains the absence of chyloperitoneum.

It is interesting to speculate on the route by which lymph and chyle are finding their way into the blood stream of this patient. In view of the fact

that all main afferent channels to the cisterna chyli and lower thoracic duct were ligated, it would appear that lymphatico-venous anastomoses within the abdomen, rather than collateral lymphatic anastomoses to the proximal thoracic duct or to the azygos vein within the chest, must be in operation.

Whether or not delay of several weeks between injury and ligation of the major lymphatic vessels favors the establishment of a more adequate collateral circulation, as it does in such vascular conditions as arterio-venous fistulae, is unknown. In view of the fact that immediate ligation of the duct following recognized injury, either within the neck or the thoracic cavity, is being practiced by modern surgeons without the development of chylothorax,<sup>12, 33, 54, 70</sup> it would appear that adequate collateral circulation already exists, and that delay in surgical repair for the purpose of establishing collateral circulation is unnecessary.

Study of the anatomy of the thoracic duct demonstrates obvious reasons for the clinical fact that right-sided chylothorax occurs more often in low injuries of the duct and left-sided chylothorax in high injuries. Persistence of embryonic ducts resulting in abnormal anatomic variations probably explains apparent exceptions to this rule.

Surgical exposure of the lower thoracic duct through the right chest is not a particularly difficult procedure. The approach may be made by incision of the mediastinal pleura following thoracotomy, as in this case,—or by the usual retropleural approach utilized in resection of the splanchnic nerves for hypertension.

In view of the fact that the lower thoracic duct and cisterna chyli are the "focal points" for the collection of the major portion of the lymph and chyle and that fibrosis and occlusion of the duct usually occurs proximal to a point of ligation or obstruction, it is our opinion that low thoracic duct ligation through the right chest is not only indicated in right chylothorax but that it would probably also prove to be effective in the treatment of left chylothorax due to high injury of the main duct, where surgical exposure of the point of injury is more difficult and hazardous.

Ligation of the duct low in the right chest should theoretically markedly reduce or entirely prevent leakage of chyle from a more proximal point of perforation, and we see no reason why this measure should not be effective in the treatment of almost all types of chylothorax, regardless of etiology.

If bilateral symmetrical ducts or other congenital abnormality be suspected, surgical approach should be on the side of the chylothorax, where a sinus will be found leading to the point of injury.

A fat meal administered several hours before operation will stimulate the flow of chyle and facilitate discovery of the incontinent duct. This procedure was used in our case and chyle continued to flow until the ducts were occluded.

A study of our findings verifies the observations of others regarding the fall of lymphocytes and eosinophiles in the peripheral blood. It is our feeling that a serious incontinence of the thoracic duct cannot long exist without a rapid and progressive fall of these constituents, especially the lymphocytes.

The explanation of the reduction of lymphocytes is obvious but of the fall of eosinophiles is obscure.

Perhaps the most significant observations that have been made in our case concern the metabolism of protein in chylothorax and will be reported in greater detail elsewhere. In general they verify the observations of others regarding the difficulty, amounting to hopelessness, of maintaining adequate serum protein concentrations by dietary means in the presence of prolonged incontinence of the thoracic duct resulting in large serum protein losses. In spite of the fact that our patient consumed a minimum of 80 Gm. of protein daily, her blood protein progressively fell to dangerous levels. The fall was not influenced by phrenic neurotomy. Following surgical ligation her protein level rapidly returned to normal without significant change in the diet.

Low protein values in chylothorax do not have the same significance as equally low values in patients suffering from hepatic failure, cancer, or diseases of the digestive tract, where there is a fundamental disturbance in protein genesis. Hypoproteinemia in chylothorax does not, *per se*, contraindicate surgery, but rather the reverse.

We do not imply that an effort should not be made to maintain nitrogen balance by high protein intake. Nitrogen balance is desirable, and can be maintained at or near normal levels in spite of large protein losses.

In view of the high mortality rates existing in chylothorax, the inadequacy of conservative treatment, and the many theoretical and practical arguments in favor of surgical ligation, it is difficult to understand the almost universal condemnation of this procedure to be found in the literature. Such a fatalistic attitude is probably based on the assumption that surgical ligation is technically impracticable when, as a matter of fact, the distal thoracic duct lies within a few millimeters of the right splanchnic nerves, removal of which have become a more or less common procedure.

A further objection to surgical ligation is probably based on the fact that most patients suffering from this condition rapidly develop low blood protein concentrations, reduced protein reserves and emaciation, and appear unable to withstand a major surgical procedure. It is our feeling that expectant and conservative treatment should be discarded within a reasonable time, before emaciation and cachexia supervene, and before the patient's condition is so extreme that major surgery is contraindicated.

#### SUMMARY AND CONCLUSIONS

1. A case of injury of the cisterna chyli during sympathectomy for hypertension, with cure of the resulting chylothorax by ligation of the thoracic duct, the cisterna chyli and all of its main afferent trunks, is described.
2. The literature of traumatic chylothorax is reviewed, and the causes, symptoms and treatment discussed.
3. The anatomy of the thoracic duct, the characteristics of chyle and the mechanics of lymph flow are reviewed.

4. Previously reported clinical, metabolic and blood cellular changes characteristic of chylothorax are verified.

5. Continuity of the thoracic duct and cisterna chyli are not essential to life, while incontinence of either is a serious hazard.

6. Lymphatico-venous anastomoses within the abdomen are adequate for the return flow of lymph and chyle following obliteration of the cisterna chyli and lower thoracic duct.

7. A period of delay between injury and operation may encourage collateral circulation of lymph and chyle, but delay of surgery for this purpose is not necessary.

8. The maintenance of normal metabolism, especially protein metabolism, by dietary methods is impossible in the presence of persistent severe chylothorax.

9. Hypoproteinemia in chylothorax is due to excessive protein loss, and is a strong indication for surgical treatment.

10. Injury of the cisterna chyli may result in chylothorax.

11. Injury of the thoracic duct and/or the cisterna chyli is a hazard of intrathoracic surgery, especially of sympathetic and esophageal surgery.

12. The prevention of chylothorax following surgical injury of the thoracic duct depends upon recognition of the injury and immediate repair or ligation.

13. Ligation of the lower thoracic duct should be effective in the treatment of most cases of left and all cases of right chylothorax, regardless of etiology.

14. Surgical approach to the lower thoracic duct and cisterna chyli should be through the right thorax.

15. Ligation of the thoracic duct and/or the cisterna chyli, when indicated, is feasible and may be a life saving procedure.

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# RECTAL STRICTURE OF LYMPHOGRANULOMA VENEREUM\*

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THERE HAVE BEEN SOME 130 ARTICLES written on lymphogranuloma venereum since 1925 dealing with various phases of the subject. The most controversial phase of the disease has been the treatment of the end result or tertiary stage. Its manifestation of severe intractable stricture involves the rectum and rectosigmoid. Occasionally the granulomatous process extends into the sigmoid and at times as far as the transverse colon. It may even show "skip areas" involving the rectum, skip the sigmoid and involve the descending colon.

Operative treatment has not yet become standardized. The literature contains numerous small series of cases and isolated case reports of various operative methods. There has actually been no evolution of basic surgical principles as yet. Some writers approach this problem from the inflammatory basis and tend to more conservative procedures, while others apply cancer principles and favor more radical operations. Where a systemic infection is present it is doubtful whether the latter principles can be considered applicable. Most authors agree on the value of colostomy preliminary to resection. However, its value in the elimination of the secondary infection and whether or not it paves the way for more conservative procedures has not been determined.

Hartmann<sup>8</sup> has had the most extensive surgical experience with this disease. At first he practiced external rectotomy, operating on 15 cases without a mortality. However, these cases continued to suppurate and many were incontinent. Following this he adopted a transanal excision of the stricture in three cases but gave up the procedure as results were unsatisfactory, due, he states, to leaving in the mucous membrane of the anal canal. Following this he began to use perineal excision, and later intra-sphincteric resection, eventually finding the latter the more satisfactory procedure. One death occurred among nine patients subjected to perineal excision and two deaths occurred in a series of 47 intrasphincteric resections. Abdomino-perineal resection was reserved by Hartmann for extensive cases only, and in six such cases there were three deaths.

DeRoche<sup>5</sup> reported 21 cases of excision of the stricture with one death. However, his results were poor, there being only three satisfactory results among eight patients followed for one year.

In 1933 Dimitriu and Stoia<sup>6</sup> reported 25 cases of abdomino-endoanal excision with preservation of the sphincter mechanism. Their method was an adaptation of a sphincter saving method of resection reported by Villard and

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Ricard<sup>14</sup> for the management of carcinoma of the rectum. The technic comprised a freeing of the sigmoid and rectum by laparotomy. The anus was then closed and a perineal incision made encircling the anus. Through this incision

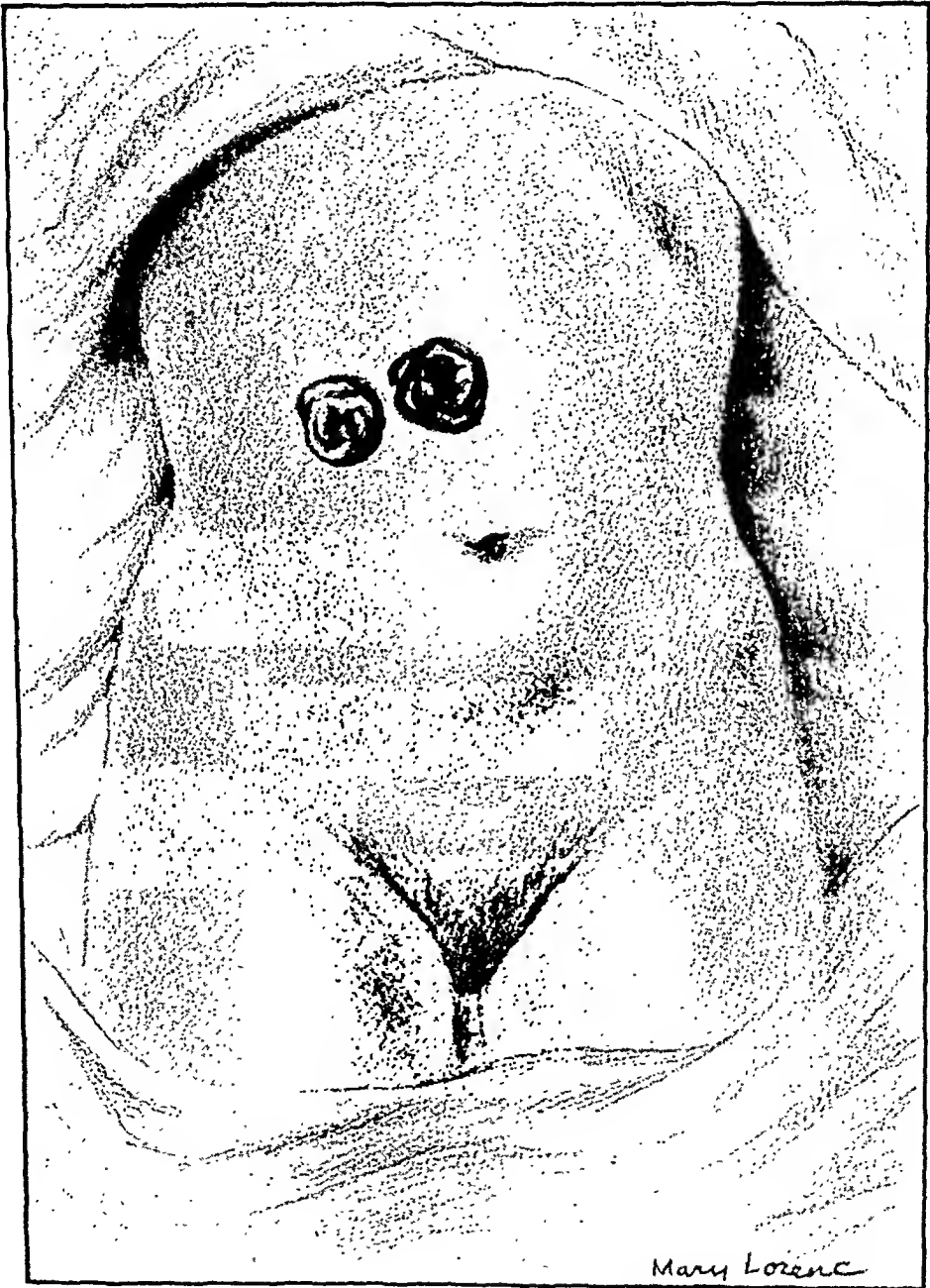


FIG. 1.—Defunctioning colostomy.

the sphincters were dilated and the rectum freed further until it could be pulled through the sphincters. The rectum was then amputated and the sigmoid pulled through the dilated sphincters and sutured to the skin. These

authors considered 19 cases cured by this method with three deaths and three recurrences. Colp<sup>3</sup> reported two cases in 1941 managed by this method.

In 1933 Keller<sup>9</sup> reported his experiences with tunnel skin grafts in the management of rectal strictures. Hair free grafts varying from one half to full thickness were sutured together to form a tunnel with the raw surface outward. A trocar and cannula were then passed through the stricture from the perianal region, and the cannula removed. A "U" shaped carrier passed through the anus, was inserted retrogradely through the cannula and used to pull up the graft. The trocar was removed and three more tunnel grafts inserted in a similar manner at equidistant points. Postoperatively these grafts were held in place by a Hagner or Pilcher bag. Two weeks postoperatively the tunnels were divided. For strictures of the anal canal the grafts were held in place by a mold of dental compound. Eight cases were reported with seven satisfactory results.

Lockhart-Mummery<sup>10</sup> favors excision of the stricture in the early cases with the Whitehead operation. For late cases perineal excision is advocated with due admonition concerning the technical difficulties.

David and Loring<sup>4</sup> reporting cases in 1936 recommend permanent colostomy, but state that cure is never obtained by this method. In 1937 Spiesman, Levy and Brotman<sup>13</sup> reported a study of 183 strictures from the Cook County Hospital. Only two of these patients came to operation, a permanent colostomy and posterior excision having been performed.

Edwards and Kindell<sup>7</sup> in 1938 reported six cases treated by the two stage Lockhart-Mummery method with one death, and mention four additional cases without a fatality. They emphasize the importance of laparotomy to determine the upward extent of the process. The second stage was performed from a few weeks to several months after colostomy, to allow patients to obtain maximum improvement in general condition.

Morris<sup>11</sup> reported one case in 1939 treated by abdomino-perineal resection of the strictured area. This patient had had a previous colostomy and when first seen the granulomatous process had involved the stoma. This necessitated preliminary resection of the colostomy stoma three months prior to abdomino-perineal resection.

In 1939 Warthen<sup>15</sup> reported a method of management in which the cul-de-sac was obliterated by the Moschowitz technic, and a left inguinal colostomy performed. The basis of this was the elimination of the hazards of dilatation by obliteration of the cul-de-sac, and putting the bowel at rest by diverting the fecal stream. Ten cases were reported with amelioration of the stricture but none of the cases had been completed.

Patterson<sup>12</sup> reported five cases in 1940 treated by permanent colostomy, and a second stage stripping out of mucous membrane from the lower sigmoid and rectum. At the time the colostomy was performed; all acute abscesses and fistulae about the anus were opened. The second stage was carried out several weeks after the colostomy.

Bacon<sup>1</sup> in 1941 agreed that radical extirpation is the procedure of choice.

TABLE I\*†

No.	Name	Age	Sex	Color	Involvement	Operations	Date	Result
1.	B.A.	33	F	C	Stricture 2 cm. above anus.	1. Colostomy. 2. Resection of stricture, end to end anastomosis of rectum. 3. Closure of colostomy.	9/24/41 3/18/42 10/27/43	Good
2.	C.B.	42	F	C	Stricture 4 cm. above anus.	1. Colostomy. 2. Abdomino-perineal resection rectum end to end anastomosis of sigmoid to anal canal. 3. Closure of colostomy.	7/15/42 6/23/43 11/7/43	Good
3.	L.C.	31	F	C	Stricture 5 cm. above anus.	1. Colostomy. 2. Resection of stricture, end to end anastomosis of rectum. 3. Closure of colostomy.	12/16/41 10/24/42 3/31/43	Good
4.	L.S.	50	F	C	Stricture 3 cm. above anus.	1. Colostomy. 2. Perineal resection unsuccessful. 3. Abdomino-perineal resection, end to end anastomosis of sigmoid to anal canal. 4. Closure of colostomy.	12/4/41 11/4/42 3/9/43	Good Died 1 year later, Ca. stomach. 4/26/44
5.	F.G.	25	F	W	Stricture 4 cm. above anus.	1. Colostomy. 2. Resection of stricture, end to end anastomosis of rectum. 3. Closure of colostomy.	7/17/44 6/15/45 4/30/47	Good
6.	M.S.	34	F	C	Stricture 3 cm. above anus, multiple fistulae with slough of perineal body, and anus opening 1 cm. from vagina.	1. Colostomy. 2. Resection of stricture, end to end anastomosis of rectum. 3. Abdomino-perineal resection of rectum, end to end anastomosis of sigmoid to anal canal. 4. Closure of colostomy.	6/14/44 1/3/45 1/29/47 7/30/47	Recurrence Good
7.	L.S.	26	F	C	Stricture 2.5 cm. above anus.	1. Colostomy. 2. Resection of stricture, end to end anastomosis of rectum. 3. Closure of colostomy.	3/31/42 3/31/43 9/15/43	Good
8.	A.W.	48	F	C	Stricture 2.5 cm. above anus. Colostomy performed elsewhere.	1. Resection of stricture, end to end anastomosis of rectum. 2. Closure of colostomy. 3. Cecostomy. 4. Plastic revision of colostomy closure. 5. Closure of cecostomy.	5/22/46 6/26/46 7/1/46 11/13/46 1/15/47	Obstruction Good
9.	C.B.	28	F	C	Stricture 4 cm. above anus.	1. Colostomy. 2. Resection of stricture, end to end anastomosis of rectum. 3. Closure of colostomy.	5/29/46 10/30/46 4/15/47	Good

\* Follow-up on these patients to July 1948.

† 16 of these cases are from the Fourth Surgical Division, Bellevue Hospital—Dr. A. S. McQuillan, Director.

1 case from Post-Graduate Hospital—Dr. J. W. Hinton, Director.

1 case from Beth David Hospital—Dr. F. W. Bancroft, Director.

# LYMPHOGRANULOMA VENEREUM

TABLE I. (Continued)

No.	Name	Age	Sex	Color	Involvement	Operations	Date	Result
10.	I.G.	43	F	C	Stricture 2 cm. above anus involving distal 2/3 of sigmoid.	1. Colostomy. 2. Perineo-abdominal resection of rectum and distal 2/3 of sigmoid. 3. Descending colon and transverse colon rotated to L.L.Q. 4. End to end anastomosis of sigmoid to anal canal.	5/22/46 3/13/47 5/16/47 2/24/48	Good
11.	R.M.	34	F	C	Stricture 3 cm. above anus.	1. Resection of stricture, end to end anastomosis of rectum.	1/17/47	Good
12.	A.E.	42	M	W	Stricture 2 cm. anus extending to splenic flexure.	1. Colostomy. 2. Perineo-abdominal resection of rectum, sigmoid, and descending colon, with mobilization and rotation of transverse colon. 3. Anastomosis of transverse colon to anal canal. 4. Closure of colostomy.	11/27/46 1/22/47 1/24/47 6/25/47	Fair
13.	C.W.	32	F	C	Stricture 2.5 cm. above anus involving entire rectum, with skip area involving descending colon up to splenic flexure, where acute perforation was present.	1. Colostomy. 2. Exploration for subphrenic abscess. 3. Resection of descending colon. 4. Resection of stricture, end to end anastomosis of sigmoid to anal canal. 5. Closure of transverse colostomy by anastomosis of its stoma to the sigmoid.	1/14/47 1/22/47 3/19/47 4/16/47 9/12/47	Good
14.	M.M.	31	F	W	Stricture 3 cm. above anus.	1. Colostomy. 2. Resection stricture, end to end anastomosis of rectum. 3. Closure of colostomy.	7/1/47 7/16/47 8/27/47	Good
15.	P.P.	25	F	W	Stricture 2 cm. above anus extending to sigmoid.	1. Colostomy. 2. Attempted perineal resection of rectum. 3. Abdomino-perineal resection of rectum, end to end anastomosis of sigmoid to anal canal. 4. Closure of colostomy.	5/7/47 8/20/47 9/24/47 11/5/47	Undetermined. Schistosomiasis in specimen
16.	J.H.	38	M	W	Stricture 4 cm. above anus.	1. Colostomy. 2. Resection of stricture, end to end anastomosis of rectum. 3. Closure of colostomy.	8/16/46 9/22/47 11/4/47	Good
17.	H.G.	23	F	C	Stricture 2 cm. above anus.	1. Perineal resection of stricture, end to end anastomosis of rectum.	10/22/47	Good
18.	R.A.	48	F	C	Stricture 3 cm. above anus, extending to peritoneal reflection. Sigmoid-colostomy performed elsewhere 10 years previously.	1. Colostomy. 2. Resection sigmoid-colostomy and end to end anastomosis of sigmoid. Resection of stricture, end to end anastomosis of rectum. 3. Closure of colostomy.	10/16/47 10/30/47 1/29/48	Good

He stated however, that procedures involving division of the peritoneal floor will give a mortality of 65 to 80 per cent. He preferred management by the two stage Lockhart-Mummery procedure. After the performance of celiotomy and abdominal colostomy, the bowel was irrigated and the patient's general condition allowed to improve. The perineal resection was then performed. In 24 cases so treated, there were no fatalities.

Barber and Murphy<sup>2</sup> reported 35 resections in 1941. Four of these were sacroperineal resections and 31 were treated by abdominal colostomy, followed by sacroperineal resection. The hospital mortality in this series was 14.3 per cent. Their early efforts attempted sacroperineal excision with a permanent sacral anus, but inability to estimate sigmoidal involvement made preliminary celiotomy and abdominal colostomy necessary prior to sacroperineal resection. Exploration and colostomy were performed 10 days prior to resection. They objected to anastomosis of the rectum on the basis that the narrowing at the anastomosis site is as troublesome as the original stricture. This has not been our experience.

Woods and Hanlon<sup>16</sup> analyzed 192 cases from the Cincinnati General Hospital in 1942 and corroborated the inefficacy of colostomy alone. Abdomino-perineal resection was done on 23 cases, and a perineal resection on nine cases without a fatality. Their experience led them to favor abdomino-perineal resection as the operation of choice.

In 1946 Wright<sup>17</sup> et al reported 26 cases operated upon by Pauchets' technic. This was a sphincter saving technic resembling that of Villard and Ricard. Colostomy was done prior to resection. Three deaths occurred in this series. Follow-up of 12 cases showed cure in all except one who had draining sinuses secondary to bone involvement.

Since previous papers have extensively described all the phases of this disease, its etiology, the primary and secondary stages, etc., we will not repeat but instead confine our discussion to the end resulting granuloma affecting the lower colon, rectosigmoid and rectum. This phase has a controversial aspect since there are so many methods of treatment suggested. The attempt should be made to eradicate the granuloma and restore the patient to normal function since we are dealing with a young age group.

The age group ranges from 20 to 40 and the colored female is most often affected. We have had a few cases in the white female and a few in the male both colored and white. All of the strictures seen in our clinic have been caused by lymphogranuloma venereum. The only other cases of stricture have had as the etiology previous anal or rectal operative procedures resulting in stricture. The stricture of lymphogranuloma venereum begins within 3 to 5 cm. of the anorectal or mucocutaneous line and goes proximally for variable distances.

The virus enters the perianal and perirectal tissue by the lymphatic route from the primary lesion in the vagina and from the inguinal lymph nodes. The perirectal and intramural lymphatics become involved and this in turn causes the inflammatory process to involve the mucosa, submucosa and muscularis

forming a firm, hard tube which by maturation of the fibroblasts causes severe contracture and stricture formation. The mucosa loses all its identity. The area is thickened and as hard as cancer tissue. The stricture tube is completely fixed by fibrous tissue to all the surrounding structures. Above the stricture

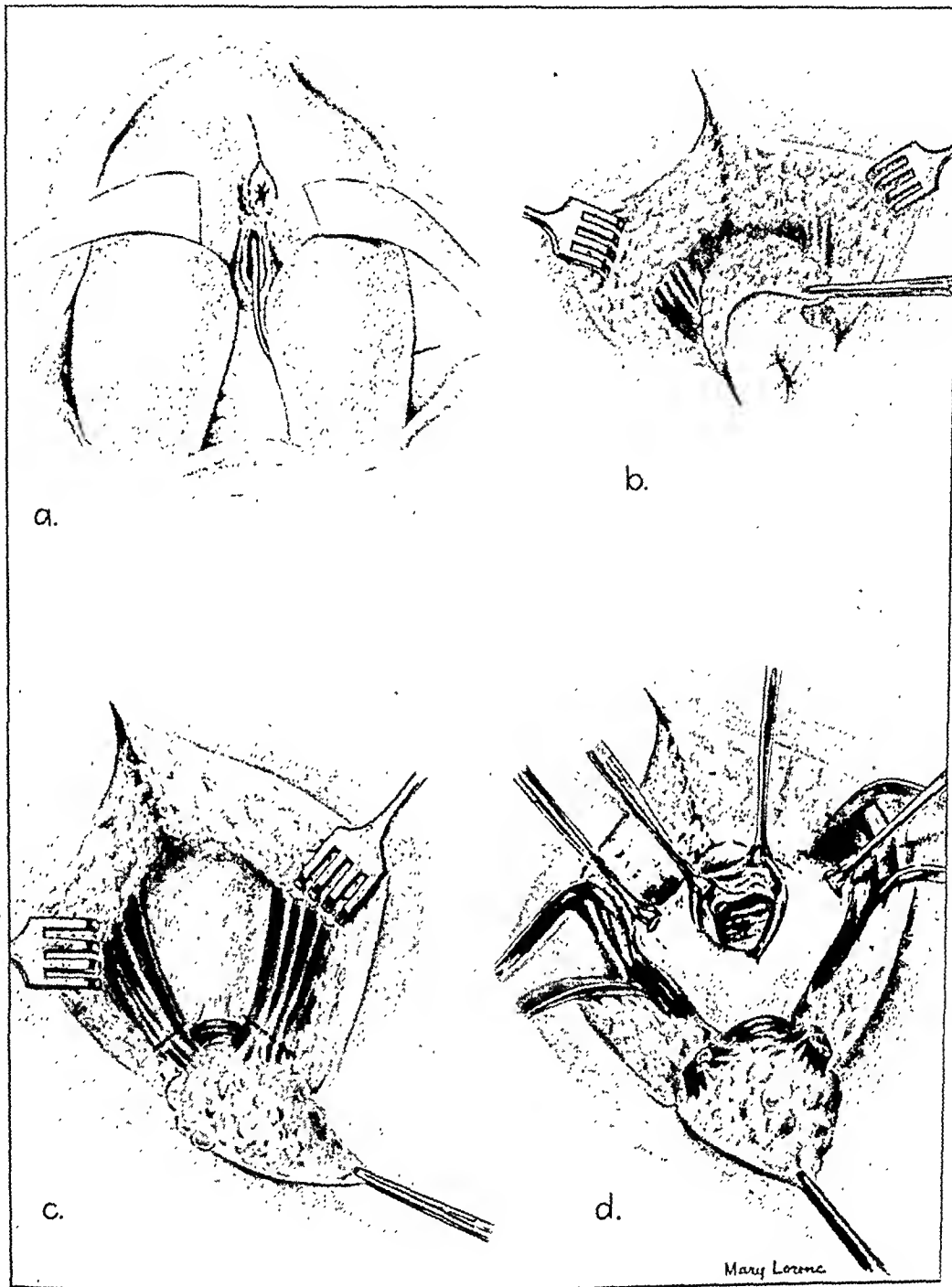


FIG. 2.—A. Position of patient and incision. B. Exposure of levator and muscles. C. Division of levators. D. Incision of fascia propia.

ulceration from secondary infection occurs causing intractable diarrhea. Fistulae form to the perianal areas and ischiorectal fossae. At times fistulae into the vagina with slough and erosion of the perineal body result in cloaca formation between the vagina and rectum. There are often hypertrophy and fibrosis of the perianal tissue and fistulae about the skin which result from long drawn out chronic inflammation.

Histologically the mucous membrane is replaced by granulation and fibrous tissue. The mass has a chronic inflammatory exudate in which the predominating cells are lymphocytes, plasma cells and foreign body giant cells. Polymorphonuclears are present due to added acute and subacute inflammation. There are no areas with tubercle formation although at one time before 1925 many of these lesions were diagnosed as tuberculosis or syphilis. This phase of the disease then is a chronic granuloma similar to other granulomata of the intestinal tract. The scarring and stricturing are irreversible processes and will not respond to any form of medical or conservative surgical treatment. One case P. P. No. 15 showed the usual pathologic changes plus eosinophilic abscesses suspicious of schistosomiasis.

The symptoms depend on the extent and degree of stricture, and on the amount of secondary infection present. The typical patient is a poorly nourished exhausted colored female. The abdomen shows varying degrees of distention depending on the tightness of the stricture. The chronic obstruction is manifested by distention, crampy pains and intractable diarrhea. The blood count shows secondary anemia and usually slight leucocytosis due to secondary infection. The plasma proteins are low and the albumin globulin ratio may be reversed. The Frei test is always positive. There is a high percentage of these patients with positive serology for syphilis as a complicating factor.

The stricture begins 3 to 5 cm. above the mucocutaneous line and runs proximally, usually ending at the rectosigmoid or low sigmoid area. Two of our cases extended to the transverse colon. One case extended to the sigmoid, then skipped an area in the descending colon for about six inches and continued on from there to the transverse colon.

The stricture results in two conditions which predicate the method of therapy selected. Functionally the lesions cause chronic obstruction, or occasionally acute obstruction. Secondly pyogenic infection accompanies the local lesion and contributes to the poor general condition of the patient. It is to these conditions that the surgeon must devote his efforts.

The first principle is the eradication of the secondary infection, and restoration of the patient to normal physiology. To accomplish this a completely defunctioning colostomy is done. It is performed 5 to 7 days after admission. In two cases, No. 11 and No. 17, where secondary bacterial invasion was not severe and no fistulae existed it was possible to do a complete resection and anastomosis in the perineum without the benefit of colostomy. This however, is unusual.

The change that occurs is almost unbelievable—the fistulae heal, the secondary infection clears up completely and the patients eat well, resulting in restoration of serum protein levels to normal, the return of normal albumin-globulin ratio and marked gain in weight with improvement in secondary anemia.

The second principle is the removal of the local focus. Cancer surgery requires radical excision but since this is only a granuloma based on virus infection its focus can be conservatively eliminated by excision of the involved

rectum or colon. A complete block dissection is not necessary. The sphincter is retained and the bowel continuity is reestablished. Lastly, the colostomy is closed and the patient is then completely rehabilitated with a normal functioning intestinal tract.

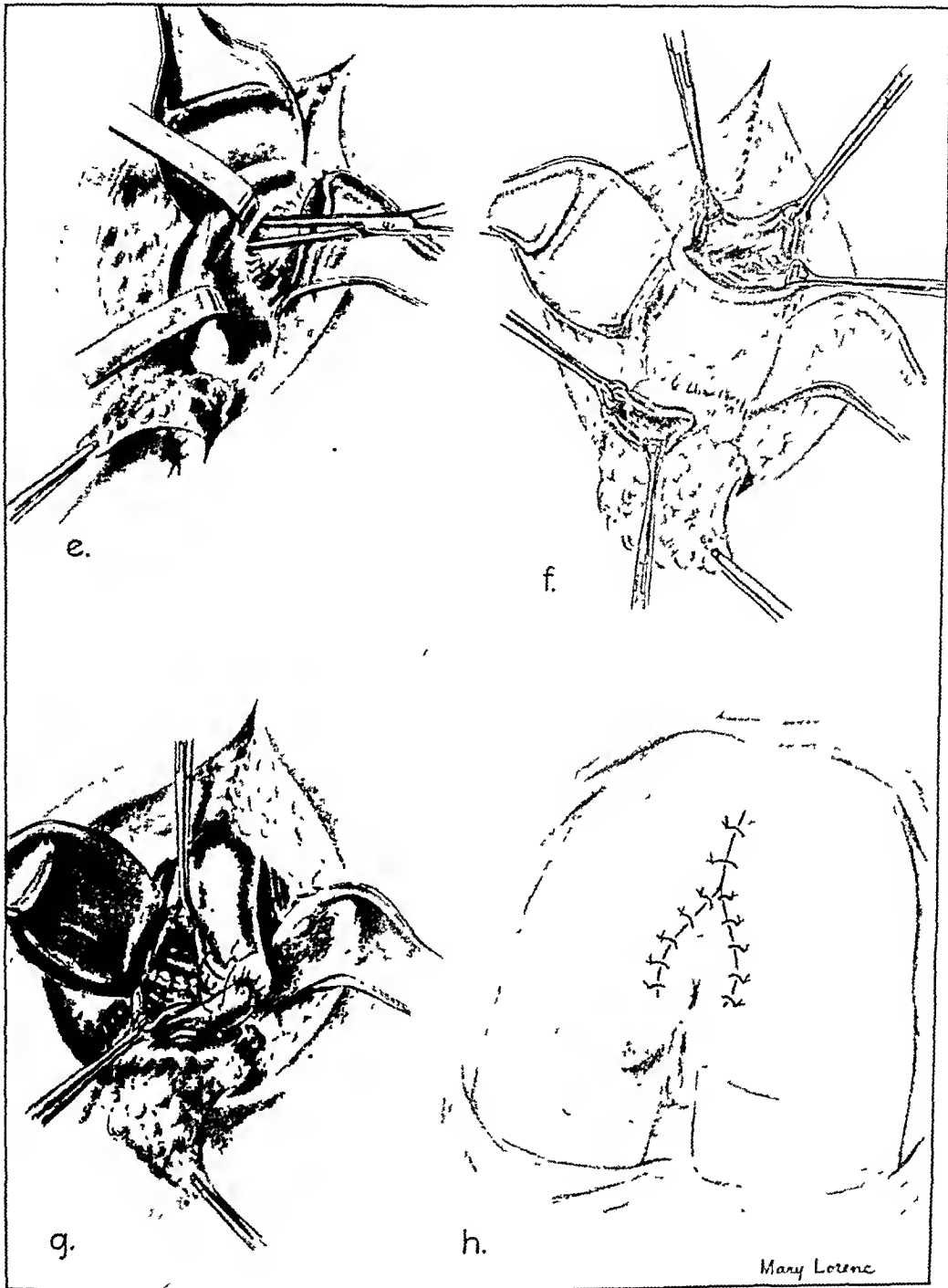


FIG. 3.—E. Mobilization of rectum and separation from vagina anteriorly. F. After resection of strictured area. G. Method of anastomosis. H. Closure of wound.

After complete healing the site of anastomosis just proximal to the sphincter shows a thin, slightly constricted area through which the finger can easily be pushed. It does not interfere with function and since all infection has been cleared away, this area does not change after healing has taken place.



## TECHNIC

The defunctioning colostomy is performed through a transverse incision midway between the umbilicus and the costal margin, extending from the midline to the lateral border of the right rectus muscle. All structures are divided transversely. The transverse colon is lifted out and cleared of omentum and appendices epiploica for a distance of three inches. The mesocolon is opened between the bowel and the marginal artery obtaining a defect 2.5 cm. in diameter. The bowel is divided between Kocher clamps with a carbolic knife. The abdominal wall is closed in layers between the divided bowel ends. The bowel is secured by suturing appendices epiploica to peritoneum, muscle, and fascia. For further security one suture is placed through the parietal peritoneum grasping an avascular spot in the transverse mesocolon so that no internal hiatus is left between the loops. A dressing is applied about the Kocher clamps to hold the two loops 4 cm. above the skin level. The proximal clamp is removed within 36 to 48 hours.

The second stage is performed one to six months later depending upon the elimination of secondary infection and the condition of the patient. The patient is placed in the prone position with the hips flexed and the buttocks held apart by adhesive. An inverted "Y" incision is made beginning over the lower end of the sacrum extending to either side of the anus to the level of a line bisecting the anus transversely. This is deepened through the skin and subcutaneous tissue to divide the levator ani muscles posteriorly, thus forming a flap which may be reflected anteriorly when the fascia propria of the pelvis or presacral fascia is incised. The rectum and rectosigmoid are then mobilized from the anterior structures (vagina, or prostate and seminal vesicles) from the promontory of the sacrum to the internal anal sphincter. The rectum is divided transversely above the stricture and just above the internal sphincter. The proximal end of the rectum is anastomosed to the anal canal using one posterior layer of interrupted medium cotton sutures and two anterior layers of the same material. The anterior layers consist of an inner layer of interrupted Connell sutures and an outer layer of Halsted sutures. The flap is replaced and the wound is repaired with interrupted cotton sutures without drainage.

The third stage is closure of the colostomy and is performed four to six weeks after resection when the anastomosis and posterior wound are well healed. Preoperative preparation consists of five days on a low residue diet and 3 Gm. of succinyl sulfathiazole every four hours. The transverse incision is reopened and the bowel ends dissected free. The peritoneal cavity is entered and the adhesions about both loops separated. Sufficient bowel is then excised from each loop to allow accurate approximation and a two layer end to end anastomosis with interrupted medium cotton sutures is performed. The mesenteric defect is sutured and the wound closed in layers.

## DISCUSSION

The technic described is adequate for most cases but in those where the lesion has extended more proximally in the colon or in the case of skip areas

## LYMPHOGRANULOMA VENEREUM

it is necessary to open the abdomen to resect the involved area. The bowel proximal to the site of resection is then brought down to the pelvis and the abdomen is closed. At the same sitting or at another stage the perineal dissection is done and the end of the proximal colon is anastomosed to the anus just above the sphincters. In two cases, No. 6 and No. 17, the anal canal was so involved that its mucous membrane had to be excised. The sphincters were incised posteriorly and the rectosigmoid pulled through the anus. We should be remiss if some of the difficulties of the described operations were not emphasized.

The colostomy offers no difficulties in performance but after its closure the transverse defect of the abdominal wall may be difficult to approximate. However, if the table is jackknifed the peritoneum and fascia may be brought together without tension. There have been no incisional hernias in this series despite this difficulty. There has been one obstruction following colostomy closure due to technical errors.

The perineal resection has offered many difficulties with other surgeons as one can glean from the literature but they are not insurmountable. The rectum and rectosigmoid are cemented to the surrounding tissue and sharp dissection must be used throughout to separate them from the vagina or prostate. At times dissection from the sacrum is like cutting through eburnated bone. Bleeding can be troublesome as ooze predominates. Fortunately this is controlled when the soft part flap is sutured back into place. A transfusion of 500 cc. to 1000 cc. of whole blood should be given during this procedure.

The proximal extent of the lesion is not always ascertainable before operation. Barium enema is often not possible as the patient cannot retain the barium. It is usually impossible to get a proctoscope through the stricture to see how far it extends. Valuable information can be obtained by the introduction of the barium suspension into the distal loop of the colostomy. Sometimes after perineal dissection has been started one finds that involvement extends above the promontory of the sacrum and abdominal dissection is necessary to complete the excision. As the entire diseased segment must be removed to effect a cure, high resection up to and including part of the transverse colon may be necessary. This is easily accomplished but bringing the proximal end down to the anus requires extensive mobilization. Two cases in this series illustrate this point:

**Case 12.**—A. E., male, age 42, white, admitted November 16, 1946, complaining of purulent rectal discharge, constipation and incontinence. Examination showed him to be poorly nourished. There was a tubular stricture of the rectum beginning at the internal sphincter. Roentgenologic examination showed a tubular narrowing of the rectum, sigmoid and descending colon up to the splenic flexure. The Frei test was positive. After a defunctionizing colostomy had been performed there was a gain of 20 pounds in weight. The rectum was freed through a sacral incision, and then the abdomen entered through a low transverse incision. The rectum, sigmoid and descending colon up to the splenic flexure were resected and the distal end of the transverse colon mobilized and buried beneath the newly constructed pelvic floor. Two days later the posterior wound

was reopened and the transverse colon anastomosed to the anal canal. The latter was accomplished with more tension than had been anticipated and during healing there was separation of the anastomosis on its posterior aspect. However, despite a tubular narrowing at the anastomosis site due to this, colostomy closure was accomplished without incident. He now has normal bowel movements with continence of gas and feces.

**Case 13.**—C. W., female, age 32, colored, admitted January 14, 1947, complaining of abdominal pain, diarrhea, and distention of the abdomen for 24 hours. For the preceding four years she had noticed ribbon stools, constipation and rectal discharge. Examination showed a cachectic female in acute shock. The abdomen was distended, board-like and tender all over. On rectal examination there was a tubular stricture beginning just above the internal sphincter. There was a leucocytosis of 21,000 with 92 per cent polymorphonuclear neutrophils. Upright abdominal films showed free air beneath the diaphragm and large bowel distention with fluid levels. Upon exploration there was free cloudy fluid coming from the left upper quadrant where a perforation was present just proximal to the splenic flexure. The large bowel was distended up to that point and collapsed distally. A transverse colostomy was performed. Convalescence was stormy and the right subphrenic space was explored for an abscess without positive findings. When her condition had improved, barium enema showed an ulcerative process involving the rectum, part of the sigmoid and the descending colon, one portion of the sigmoid being uninvolved by the process. Through a left transverse incision the splenic flexure, descending colon, and involved sigmoid were resected, planting the proximal end of the normal sigmoid in the lateral angle of the wound. One month later the rectum was resected and the normal sigmoid anastomosed to the anal canal. Gastro-intestinal continuity was reestablished by anastomosing the colostomy stoma to the proximal end of the sigmoid.

The anastomosis in the perineum is not difficult. The area is well exposed so that it may be done accurately. There have been no fistulae resulting from this anastomosis. The closure of the perineum usually results in primary union and drainage has not been necessary. Continence is established after this type of procedure.

All of these patients with completed operation have been restored to normal health. The intestinal tract is intact, there is complete sphincter control and fistulae are solidly healed. There is no protruding mucous membrane to cause constant moisture. The results have justified the extensive procedures.

The morbidity fortunately has been insignificant even in those cases where extensive colonic resection had to be done in stages in order to shift segments of the colon nearer to the pelvis for an anastomosis to the anus. In one case cited where the transverse colon was brought down and anastomosed to the anus, the posterior portion of the suture line pulled apart slightly and filled in with fibrous tissue but a good continuity of mucous membrane was established.

We are convinced that a complete resection of the diseased area results in cure. In Case No. 6 the point is illustrated. She was resected perineally and after healing a new tubular stricture promptly formed completely closing the bowel. At the second operation the resection was carried higher removing the entire rectum and pulling the sigmoid through the anus. Since the entire diseased segment has been excised there has been no recurrence.

There have been no fatalities in the 18 patients subjected to resection. Two of these patients are awaiting closure of the transverse colostomy.

SUMMARY

1. The rectal stricture of lymphogranuloma venereum is a common disease in a large city hospital especially among the negro race.
2. The surgical principles of management of chronic granulomata are applicable namely, physiologic rest of the part, extirpation of the diseased segment, and restoration of intestinal continuity.
3. A completely defunctioning type of colostomy is the first phase of treatment.
4. Perineal excision and primary anastomosis has proven an efficient method of extirpating the granuloma.
5. Extensive excision of the granuloma may be necessary, even as far as the transverse colon with anastomosis of this segment to the anus.
6. This method has been used in 18 cases with low morbidity and no mortality.
7. Arrest of the process and sphincter control have been achieved in all cases.

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# TETRAETHYL AMMONIUM CHLORIDE—ITS EFFECTS ON SURFACE TEMPERATURES OF EXTREMITIES IN PERIPHERAL VASCULAR CONDITIONS\*

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THE PURPOSE OF THIS ARTICLE is to report the effects of tetraethyl ammonium chloride on the surface temperatures of extremities. It shows that these effects are unsuitable as diagnostic criteria in peripheral vascular disease. The experiments which led to this conclusion were carried out as follows:

For the satisfactory clinical estimation of vasoconstrictor tone in extremities, one must have a method upon which he may rely to give a true, complete and dependable vasoconstrictor paralysis. The test should be, if possible, ambulatory and able to be completed at one sitting. The reports of Berry, Campbell, Lyons, Moe and Sutler,<sup>1</sup> gave hope that injections of tetraethyl ammonium chloride, by producing "autonomic blockade," would replace previous methods of estimating the vasoconstrictor element in peripheral vascular disease. If the drug were efficacious, it would furnish the desired data simultaneously on all four extremities, eliminating the discomfort attending blocking peripheral nerves, or the danger and discomfort of subarachnoid block. The present study was made for the purpose of comparing the surface temperature effects of the drug with that produced by peripheral nerve block. The latter method has been proven accurate and dependable over a long period and in many hands, and in the personal experience of the author with over 400 vasomotor studies.

A group of patients suffering from various types of peripheral vascular and central nervous system disorders were used as subjects. Food, drink and tobacco were ordered eliminated on the morning of the test. Each patient was placed recumbent for one hour or more in a specially constructed constant temperature room, with the lower extremities exposed from the upper thighs to the toes, and the upper extremities from the upper arm to the fingers. The temperature of the room did not vary significantly throughout the individual experiment, but the room temperature varied with the different subjects from 16.7° C. to 20° C. The surface temperatures of all four extremities were then measured at certain definite areas with the Tycos Dermatherm. A 10 per cent aqueous solution of tetraethyl ammonium chloride (100 mg. per cc.) was then injected intravenously over a period of from one to seven minutes. Two hundred mg. of the drug were used cautiously in the first case, but in the remainder, the drug was administered until the pulse *volume* showed a marked

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# TETRAETHYL AMMONIUM CHLORIDE

decrease, or until 500 mg. had been given. In some, its administration had to be slowed or temporarily discontinued while the weakened pulse volume returned to normal. The doses of tetraethyl ammonium given are as shown in Chart I. All but one patient received 300 mg. or more. In Cases 3 and 4,

## Comparative Effects of TEAC and Peripheral Nerve Block on Surface Temperatures

F.M. Age 68 M.

Arteriosclerosis  
Hypertension

Upper Extremities						
	After 135" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	20.9	20.4	21.0	21.0	30.4	30.7
2	20.0	20.4	21.0	20.5	30.4	30.8
3	19.9	20.0	21.0	20.7	30.7	30.9
4	19.9	19.9	21.0	20.9		
5	20.1	20.3	20.9	20.8		
Palm	22.5	23.0	23.1	22.7		
Dorsum	23.0	22.8	22.5	22.0		
Wrist	24.9	24.6	24.0	23.2		
Midforearm	26.9	26.9	25.5	25.6		
Below Elbow	27.9	27.8	27.7	26.7		
Above Elbow		27.4		26.5		
Lower Extremities						
	After 135" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.7	21.8	25.3	25.3	30.4	30.8
2	21.1	21.3	24.8	25.3	30.3	29.2
3	20.8	21.2	25.3	24.5	30.2	29.8
4	21.2	21.2	23.3	25.1 *	30.2	30.7
5	21.2	21.7	21.8	23.8	29.8	29.8
Sole	24.2	23.8	23.5	23.6		
Heel	23.2	23.3	22.5	22.5		
Ankle	26.8	26.2	25.8	23.4		
Midleg	27.4	27.3	26.5	26.3		
Below Knee	25.8	25.3	24.8	23.8		
Above Knee	27.9	26.8	26.8	26.8		

FIG. 1.—F. M. Peripheral arteriosclerosis. Surface temperature after exposure, maximum surface temperature after tetraethyl ammonium and after nerve block. Note that in the upper extremities after tetraethyl ammonium there were no significant rises but after median nerve block all of the areas reached normal vasodilatation level. In the lower extremities after tetraethyl ammonium there were slight to moderate rises, whereas, block produced high sub-maximal temperatures. For further details of history and examination, see text.

the original dose of 300 mg. was supplemented by an additional dose of 200 mg.; in Case 6, 300 mg. were given as a second dose following an initial dose of 200 mg. These secondary doses had no apparent effect. When the administration of the drug was completed, the surface temperatures of all four extremities were measured at the selected sites at intervals of approximately five to ten minutes, in some for 30 minutes, in others until each individual site reached its maximum temperature. Without changing the position of the patient or the temperature of the room, vasoconstrictor paralysis was then produced at the same sitting in many extremities by procaine nerve block. Surface temperatures of the blocked zones were then measured at 10-minute intervals until each site reached its maximum temperature.

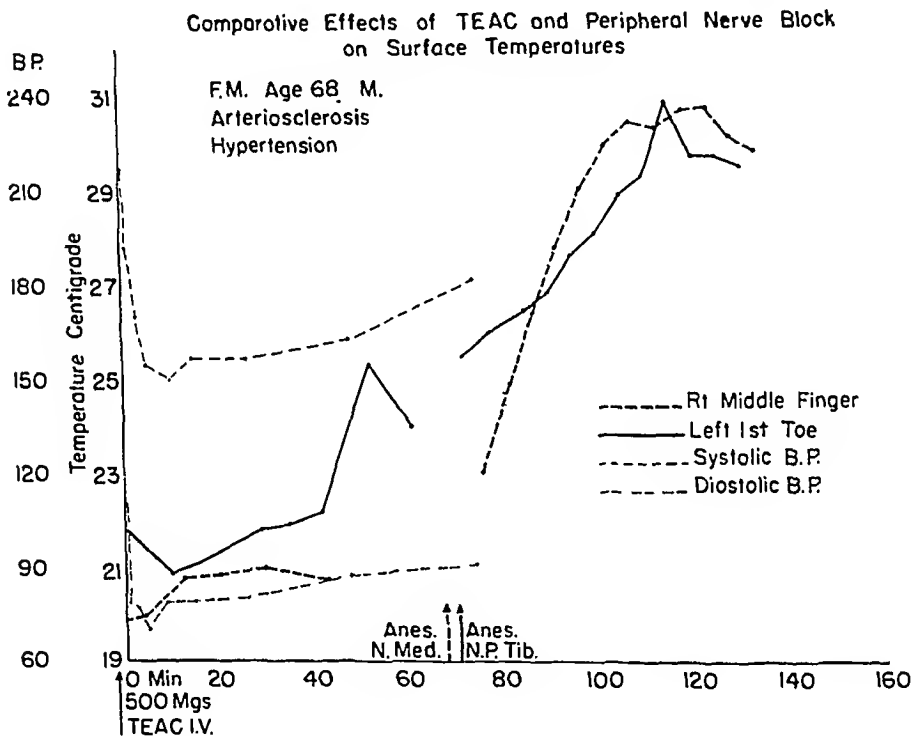


FIG. 2.—Same experiment as Fig. 1. The graph shows the results of the experiment in a single digit of the upper and lower extremities. After tetraethyl ammonium, the finger showed no significant change. The toe had an initial fall followed by a rise of  $25.3^{\circ}$  C. After nerve block, both finger and toe reached the normal level.

Of the total of 18 patients tested, nine were selected to be the subject of this report. The remainder are all cases of degenerative arterial disease and will become the material for an additional publication. The surface temperature effect of tetraethyl ammonium was measured in all 36 extremities in these nine patients; in 21 of these 36 extremities the effect was compared with that produced by novocaine block of the median or posterior tibial nerve; in one extremity, with block of the lumbar sympathetic chain. In one case the effect of tetraethyl ammonium was noted in the sympathectomized lower

extremities. It should be noted that in Cases 1, 4, 5 and 6, there was no evidence of arterial disease and normal responses to complete vasoconstrictor paralysis were to be expected. A similar result was also looked for in the upper extremities of all the cases except Case 2, since with this exception they showed no clinical evidence of arterial disease.

The maximum surface temperatures of the digits after the administration

Comparative Effects of TEAC and Peripheral Nerve Block  
on Surface Temperatures

R.B. Age 52 M.                      Thromboangiitis Obliterans

Upper Extremities

	After 50" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	24.2	24.5	29.6	29.4	30.9	30.5
2	24.2	23.3	30.3	28.7	31.0	30.1
3	22.6	22.4	29.0	29.4	31.0	31.8
4	22.9	22.0	28.5	27.8	30.3	31.8
5	22.3	22.1	28.6	28.7		
Palm	27.4	27.8	30.1	29.9		

Lower Extremities

	After 90" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.0	19.9	23.1	22.5	31.5	30.7
2	20.6	20.5	22.8	23.0	31.9	30.4
3	21.5	20.3	23.4	22.5	31.5	29.3
4	21.3	20.0	23.8	22.3	32.0	32.0
5	21.9	20.4	24.1	23.7	32.1	31.0
Sole	23.1	22.6	24.3	23.7	31.3	31.0
Heel	22.4	22.0	23.3	24.9	31.6	31.0

FIG. 3.—R. B. Thromboangiitis obliterans. Surface temperature after exposure and maximum temperature after tetraethyl ammonium chloride and after nerve block. In the upper extremity after tetraethyl ammonium there was a good rise of temperature but not to the normal level; after nerve block there was a normal level. In the lower extremity after tetraethyl ammonium there was only a slight rise, whereas, after block there were normal levels in all but the left 3d toe which reached 29.3° C. For further details of history and examination, see text.

of tetraethyl ammonium, the maxima reached after peripheral nerve block, the clinical diagnosis and other pertinent case details are shown in Chart I. The range of surface temperatures in each experiment is here indicated by noting the lowest and highest maximum readings among the five digits. The thermocouple readings were corrected by adding or subtracting 0.3° C. for each



degree centigrade that the room temperature was respectively below or above 20° C.

## CASE REPORTS

The following two cases show typical results of the experiment:

**Case 1.**—F. M. (Case 8—Table I) Male diabetic. Age 68. Degenerative arterial disease.

TABLE I

Case No.	Initial	Age	Sex	Diagnosis	Min-utes Expos.	Mg. TEAC. I.V.	Ex-trem-ity	Surface Temp. After Expos.		Max. Surface Temp.			
								Low-est	High-est	After TEAC.		After Block	
										Low-est	High-est	Low-est	High-est
1	J.S.	23	M	Spastic quadriplegia. No evidence of arterial disease	65	400	RU	21.8	23.2	27.8	28.9	30.0	31.4
					65		LU	21.7	23.3	24.0	26.5	31.5	32.5
					65		RL	18.2	18.7	19.4	20.3	31.2	31.4
					65		LL	18.8	19.6	19.3	20.2	30.8	31.4
2	R.B.	52	M	Thromboangiitis obliterans	50	500	RU	22.3	24.2	28.5	30.3	30.3	31.0
					50		LU	22.0	24.5	27.8	29.4	30.1	31.8
					90		RL	20.6	21.9	22.8	24.1	31.5	32.1
					90		LL	19.9	20.5	22.3	23.7	29.3	32.0
3	M.L.	29	M	Thromboangiitis obliterans	120	300	RU	20.6	21.1	21.5	22.0	30.5	31.8
					120		LU	20.1	20.6	20.7	22.0		
					120		RL	24.0	25.5	24.3	26.8	24.3	27.3
					120		LL	25.0	27.0	28.3	29.8		
4	G.B.	42	F	Thrombophlebitis. Hypertension. No evidence of arterial disease	35	300	RU	21.2	22.5	28.1	30.9		
					35		LU	21.5	23.4	30.1	31.4		
					35		RL	22.2	22.6	30.0	30.5		
					35		LL	22.0	22.4	30.1	30.8		
5	M.C.	47	F	Thrombophlebitis. No evidence of arterial disease	63	350	RU	19.0	22.8	20.1	20.8		
					63		LU	19.1	20.3	20.4	21.1		
					63		RL	20.9	21.9	22.8	24.0		
					63		LL	21.7	22.2	25.2	27.0	32.0	*32.8
6	E.M.	49	F	Thrombophlebitic edema. No evidence of arterial disease	120	200	RU	18.9	19.9	22.9	27.4	30.2	31.0
					120		LU	18.9	19.9	22.8	23.4	30.8	31.2
					120		RL	21.1	21.6	27.8	30.4		
					120		LL	19.5	20.2	27.8	30.7	25.9	*32.0
7	J.R.	61	M	Degenerative arterial disease	45	400	RU	20.3	20.5	22.3	22.5		
					45		LU	20.9	21.7	24.7	25.2		
				Sympathectomized.....	60		RL	23.3	28.0	24.5	29.0		
					60		LL	25.8	29.6	26.3	30.4		
8	F.M.	68	M	Degenerative arterial disease	135	500	RU	19.9	20.9	20.9	21.0	30.4	30.7
					135		LU	19.9	20.4	20.5	21.0	30.7	30.9
					135		RL	20.8	21.7	21.8	25.3	29.8	30.4
					135		LL	21.2	21.8	23.8	25.3	29.2	30.8
9	G.A.	62	M	Degenerative arterial disease	40	300	RU	21.0	22.5	21.3	22.8	31.0	31.3
					40		LU	21.5	24.0	20.8	23.7	30.0	31.2
					80		RL	19.5	20.0	19.9	20.6	24.0	30.3
					80		LL	20.1	20.5	20.0	20.5	26.6	30.3

Where blocks are indicated, all were on peripheral nerves except the left lower extremity of case No. 5 in which a paravertebral lumbar sympathetic block was done.

\* Nerve block incomplete.

# TETRAETHYL AMMONIUM CHLORIDE

*Chief Complaint:* Pain in arches and toes of both feet. No claudication.

*Examination:* Right dorsalis pedis pulse  $+++$ , left  $+$ ; both posterior tibial pulses absent. Has elevation ischemia on the left, dependent rubor of both feet, worse on the left. Roentgenograms show marked calcification of arteries of feet and legs.

Figure 1 shows results of exposure, tetraethyl ammonium and nerve block on surface temperatures.

In the upper extremities after tetraethyl ammonium, there were no significant rises, but the temperature after median nerve block reached normal levels.

In the lower extremities after tetraethyl ammonium, there were slight to moderate rises, whereas block produced high sub-maximal temperatures, indicating early vasoconstrictor recession.

Comparative Effects of TEAC and Peripheral Nerve Block  
on Surface Temperatures

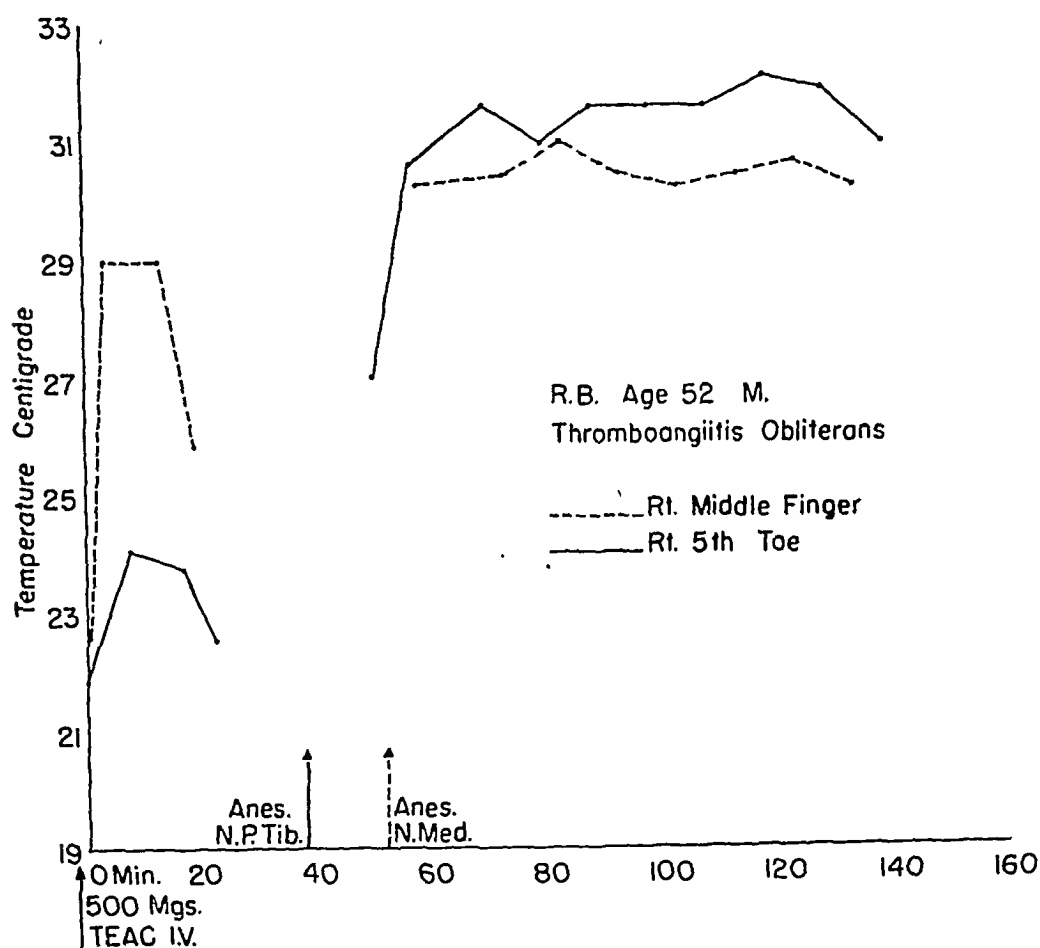


FIG. 4.—Same experiment as Fig. 3. The graph shows the result of the experiment in a single digit in the upper and lower extremities. After tetraethyl ammonium the surface temperature of the finger rose to  $29.0^{\circ}\text{C}$ , the toe to  $24.1^{\circ}\text{C}$ . After nerve block, the finger rose to  $31.0^{\circ}\text{C}$ , the toe to  $32.1^{\circ}\text{C}$ .

If tetraethyl ammonium alone were used, vasoconstrictor recession due to occlusive arterial disease would be diagnosed in all four extremities, advanced in the upper, moderately advanced in the lower extremities. Actually, the vasoconstrictor element was normal in all digits but the left 2nd and 3rd toes where it was submaximal.

Figure 2 shows results of the experiment in a single digit of the upper and lower extremities.

**Case 2.**—R. B. (Table I) Male. Age 52. Thromboangiitis obliterans.

*Chief Complaint:* Claudication, right leg, 4 years. No ulceration.

*Examination.* Right posterior tibial and popliteal pulses 0; all other lower extremity pulses +++. Elevation ischemia + on the right, 0 on the left. Dependent rubor +, both feet. Right radial artery +; left +++. Right ulnar artery +++; left 0.

Figure 3 shows results of exposure, tetraethyl ammonium and nerve block on surface temperature.

In the upper extremities after tetraethyl ammonium, there was a good rise of temperature but not to the normal level. After nerve block a normal level was reached.

In the lower extremities after tetraethyl ammonium, there was only a slight rise, whereas after block there were normal levels in all but the left 3rd toe which reached 29.3° C.

Were tetraethyl ammonium alone used, one would diagnose early vasoconstrictor recession in the upper extremities and advanced vasoconstrictor recession in the lower extremities, whereas the vasoconstrictor element was normal in all digits but the left 3rd toe.

Figure 4 shows the results of the experiment in a single digit of the upper and lower extremities.

#### SUMMARY OF RESULTS

Intravenous administration of tetraethyl ammonium chloride was followed in certain extremities by a variable rise of surface temperature. In one case (No. 4) tetraethyl ammonium produced a rise of surface temperature to the average normal vasodilatation level in many digits, in other digits to somewhat below this level. No nerve block was done on this patient so that the actual maximum temperature after complete vasomotor paralysis is not definitely known. In all cases in which nerve block was done in addition to the administration of tetraethyl ammonium, any rise of temperature following tetraethyl ammonium was below that proven possible by nerve block. The discrepancy reached 12.2° C. in Case 1; in others, differences of from 8°-10° C. were common. Some digits which had minimal or absent temperature rises following the drug, were proven by nerve block to have the ability to reach or exceed the normal vasodilatation level of 30.5° C. The temperatures of some digits actually fell after tetraethyl ammonium. When a rise of temperature was produced by the drug, the duration of a satisfactory effect was short, averaging about 15 minutes.

#### CONCLUSIONS

1. The surface temperature effects following the intravenous administration of tetraethyl ammonium chloride were measured under controlled conditions in all 36 extremities in nine patients, eight of whom had various types of peripheral vascular disease. In 21 of these extremities comparison was made with the surface temperature effects of peripheral nerve block; in one with lumbar sympathetic block.
2. The effects of tetraethyl ammonium are variable, undependable, usually incomplete and of short duration.
3. Therefore, tetraethyl ammonium is unsuitable as a diagnostic method in estimating the degree of vasoconstrictor tone in the extremities.

4. These experiments cast doubt on the efficiency of the drug as a vasodilating agent in peripheral vascular disease.

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# TETRAETHYL AMMONIUM CHLORIDE— ITS EFFECTS ON SURFACE TEMPERATURES OF ARTERIOSCLEROTIC EXTREMITIES\*

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IN THE EARLY YEARS following the discovery of the peripheral vascular effects of paravertebral sympathetic ganglionectomy, the presence or absence of peripheral arterial disease was thought to depend on the degree of vasoconstriction as demonstrated by appropriate tests. We now know that this concept was erroneous and that advanced occlusion may occur in the major peripheral arteries of extremities which still maintain a normal or high vasoconstrictor element. Vasoconstriction is not synonymous with "spasm." It occurs in extremities with normal peripheral vessels, and is also present to a normal or high degree in the early stages of chronic occlusive arterial disease. It is only in the advanced stages of chronic occlusive disease that the vasoconstrictor element has disappeared; all gradations exist between the occlusive disease with normal vasoconstriction and the occlusive disease with vasoconstriction absent.

The degree of vasoconstriction is usually determined by the effect of temporary vasoconstrictor paralysis on the surface temperatures of extremities. This vasoconstrictor paralysis may be produced by general anesthesia, spinal anesthesia, paravertebral sympathetic block, peripheral mixed nerve block or Landis-Gibbon warm water extremity immersion. On the basis of a personal experience with over 400 vasomotor studies over a period of 17 years, the author considers procaine block of the mixed peripheral nerves as the most accurate and reliable.

The reports of the production of "autonomic blockade"<sup>2, 3, 4, 5</sup> by tetraethyl ammonium chloride stimulated the author to compare the results of this drug with vasoconstrictor paralysis produced by methods proven by years of experience to be accurate and dependable, especially by procaine block of mixed peripheral nerves. In a discussion of the article by Collier and his associates<sup>5</sup> on the effects of tetraethyl ammonium, De Bakey<sup>6</sup> reports that local nerve and regional sympathetic block invariably produced increases in skin temperature two to six times greater than that caused by tetraethyl ammonium bromide given intravenously, and that the duration of elevation following block was in every instance considerably more prolonged than the elevation following tetraethyl ammonium. Plethysmography corroborated these results. Later he reported such findings in a normal individual.<sup>7</sup> The author's results on a group

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of subjects suffering from various types of peripheral vascular disease have been reported elsewhere.<sup>8</sup> In that article, the reader will find a full description of the method used in this study.

The present report deals only with the effects of tetraethyl ammonium chloride on 12 cases of degenerative arterial disease, in two of which (Cases 11 and 12) the lower extremities had been previously sympathectomized. The

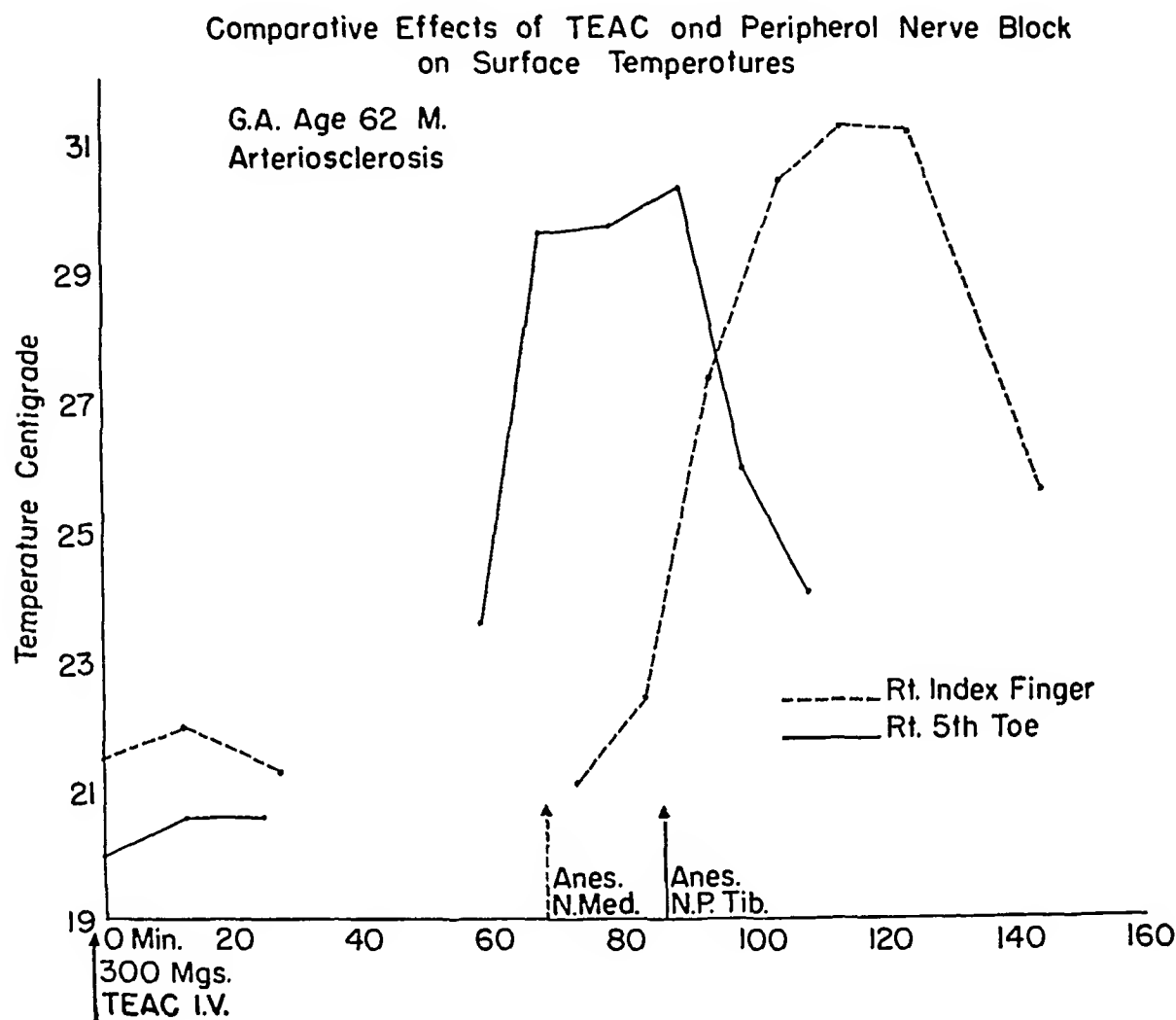


FIG. 1.—Case 3. G. A. Age 62. M.

Claudication of both legs, 2 months, no ulceration or gangrene.

*Examination:* Dorsalis pedis pulses +++, posterior tibial +, popliteal and femoral pulses +++. No elevation ischemia either side; dependent rubor ++, both sides. Marked trophic disturbances. Marked calcification of foot and leg arteries by x-ray. Mild diabetic.

Neither the finger nor the toe showed any appreciable effect from tetraethyl ammonium. After median and posterior tibial block, both the finger and the toe reached normal vasodilatation level.

important data obtained in this study are set forth in Table I, which gives the dosage of the drug, the surface temperatures of the digits after exposure and the maximum surface temperatures of these digits after tetraethyl ammonium chloride and in most cases after peripheral nerve block. To afford the reader a clearer picture of the results, the lowest and highest maximum temperatures

# Comparative Effects of TEAC and Peripheral Nerve Block on Surface Temperatures

G.A. Age 62 M.

Arteriosclerosis

## Upper Extremities

	After 40" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	22.5	24.0	22.8	23.7	31.0	30.0
2	21.5	23.5	22.0	21.7	31.3	31.2
3	21.0	23.0	21.5	21.4		31.0
4	21.0	22.0	21.5	21.1		
5	21.5	21.5	21.3	20.8		
Palm	25.5	25.5	26.5	26.0		
Dorsum	25.5	26.0	26.1	24.7		
Wrist	26.5	27.0	26.5	27.3		
Midforearm	27.0	28.5	28.3	28.5		
Below Elbow	28.5	28.5	28.0	27.0		
Above Elbow		29.5		30.0		

## Lower Extremities

	After 80" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	19.5	20.3	19.9	20.3	24.0	29.8
2	20.0	20.0	20.1	20.0	27.5	26.6
3	20.0	20.5	20.4	20.5	28.2	28.8
4	20.0	20.1	20.6	20.1	28.6	28.1
5	20.0	20.4	20.6	20.4	30.3	30.3
Sole	22.5	21.4	20.0	21.8	29.3	29.2
Heel	22.5	22.1	22.3	22.1	30.0	29.6
Ankle D	23.0	24.0	22.3	24.0		
Midleg	25.0	24.3	24.3	24.3		
Below Knee	26.5	24.0	24.7	24.0		
Above Knee	26.5	25.5	26.5	25.9		

FIG. 2.—Case 3. G. A. Age 62. M.

*Upper Extremities:* After tetraethyl ammonium there was no significant rise of surface temperature in the digits on the right; an actual fall of surface temperature of the left digits of from 0.3° C. to 1.6° C. After median nerve block there was a normal level in the right 1st and 2nd digits, and in the left 2nd and 3rd digits. The left 1st digit rose to 30° C., slightly under the normal level but within the limits of error of the experiment. The right 3rd digit was not completely anesthetized.

*Lower Extremities:* After tetraethyl ammonium there was no significant rise of surface temperature on either side. After posterior tibial block there was moderate to good rise on both sides, better on the left, but in no case to the normal dilatation level. The block, however, produced temperature rises varying from 9.9° C. to 4.1° C. higher than that produced by tetraethyl ammonium.

Were tetraethyl ammonium alone used, advanced vasoconstrictor recession would be diagnosed in all four extremities. Actually, the vasoconstrictor response was normal in the upper extremities, moderately decreased in the lower extremities.

of the digits of that particular extremity are noted. In addition, five cases were selected for more detailed description of the effects of tetraethyl ammonium chloride. These represent various stages of development of peripheral arterio-sclerosis; in one, the lower extremities had been previously sympathectomized.

Comparative Effects of TEAC and Peripheral Nerve Block  
on Surface Temperatures

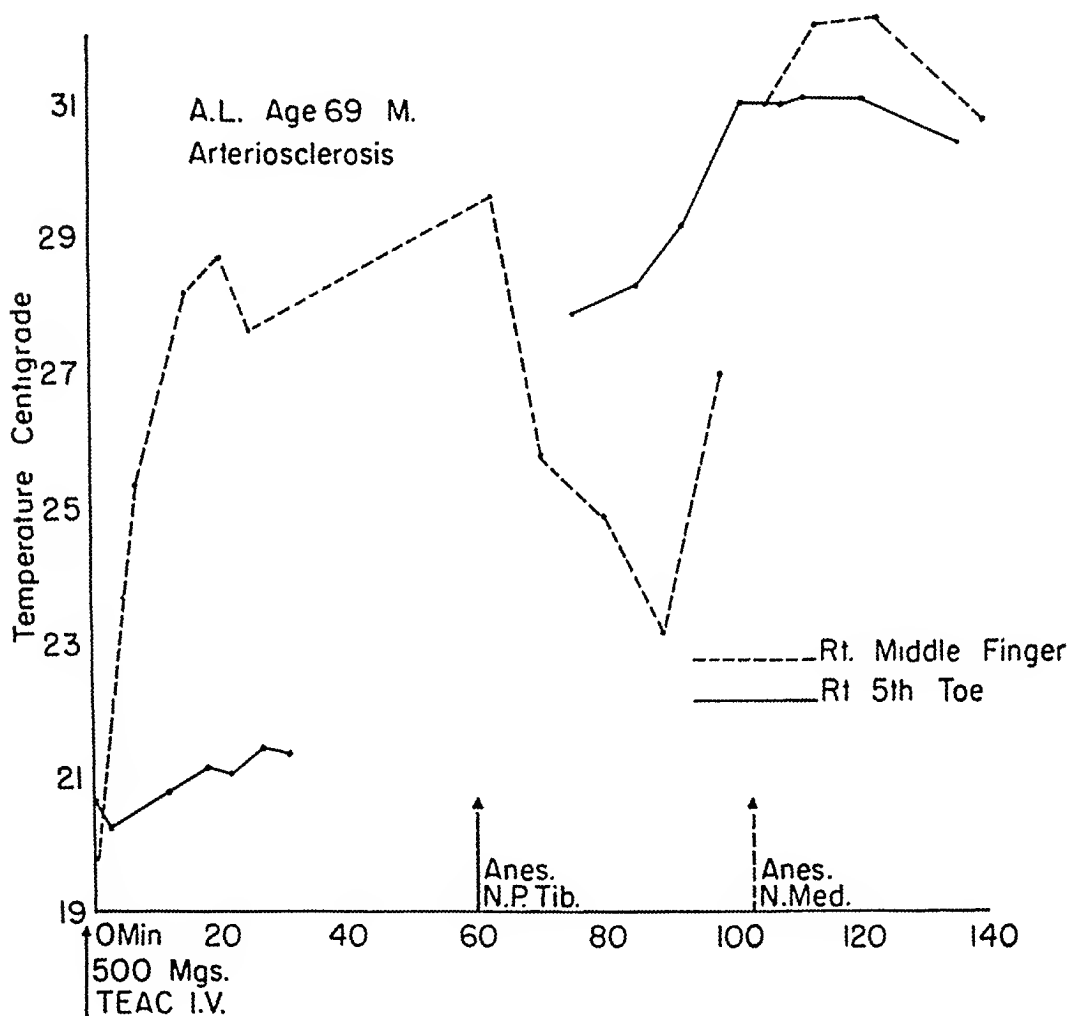


FIG. 3.—Case 4. A. L. Age 69. M.  
Claudication of the left calf after walking  $1\frac{1}{2}$  blocks; "pins and needles" of left toes and heel for 3 to 4 weeks.  
*Examination:* Femoral pulses +++; all other pulses both sides absent. No elevation ischæmia. Dependent rubor + on the left; 0 on the right.  
After tetraethyl ammonium chloride there was a marked rise of temperature in the finger, but  $3.6^{\circ}$  C. below the level reached after block; there was no significant rise of temperature in the toe, yet the temperature after nerve block reached  $31.1^{\circ}$  C.

These detailed data are reported in a series of figures—a graph and a table for each case. The graphs give a visual impression of the effects of the drug and nerve block on single digits of the extremity. The tables give these data on all the digits of that patient and of the other sites selected for surface temperature measurements.



Comparative Effects of TEAC and Peripheral Nerve Block  
on Surface Temperatures

A.L. Age 69 M.

Arteriosclerosis

## Upper Extremities

	After 75" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	20.4	20.9	27.7	23.8	31.1	31.8
2	19.9	20.9	28.2	26.2	32.0	32.1
3	19.8	20.8	28.7	27.7	32.3	32.2
4	19.7	21.2	29.2	28.7		
5	19.8	21.3	29.3	29.3		
Palm	23.3	23.9	29.3	29.7		

## Lower Extremities

	After 75" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.3	21.8	22.2	22.2	29.9	26.9
2	20.6	22.1	21.7	22.4	30.4	26.7
3	20.7	22.8	21.3	23.6	29.9	26.2
4	20.7	24.8	21.3	25.6	30.5	27.5
5	20.8	25.2	21.2	25.6	31.1	27.3
Sole	24.3	25.3	25.3	28.3	31.3	28.1
Heel	24.0	26.4	24.3	25.7		
Ankle	27.3	27.3				
Midleg	26.9	26.8				
Below Knee	25.8	27.9				
Above Knee	28.3	27.3				

FIG. 4.—Case 4. A. L. Age 69. M.

*Upper Extremities:* After tetraethyl ammonium chloride there was a good but incomplete rise of surface temperature in most digits. Median nerve block produced normal levels or better in each digit anesthetized.

*Lower Extremities:* After tetraethyl ammonium chloride there were minimal rises of temperature. After block the temperatures of the right side varied from 29.9° C. to 31.3° C., at or slightly below the normal level; those of the left side varied from 26.2° C. to 28.1° C., showing evidence of moderately advanced recession of vasoconstriction due to occlusive arterial disease.

If tetraethyl ammonium chloride alone were used the normal response in the upper extremities would be overlooked; the right lower extremity would have been judged to have advanced arterial disease without vasoconstriction, whereas there was a submaximal vasoconstrictor element still present; and in the left lower extremity, the rise to a moderate range would have been missed. In both lower extremities sympathectomy would probably have been denied the patient, whereas block indicates without question that following sympathectomy a marked increase in temperature would follow on the right and a moderate increase on the left.

SUMMARY

Tetraethyl ammonium chloride was given intravenously to 12 patients all of whom were suffering from peripheral arteriosclerosis; the lower extremities of two of these (Cases 11 and 12) had been previously sympathectomized. The effect of tetraethyl ammonium chloride on the surface temperatures was measured in all 46 extremities; in 31 of these surface temperatures were also

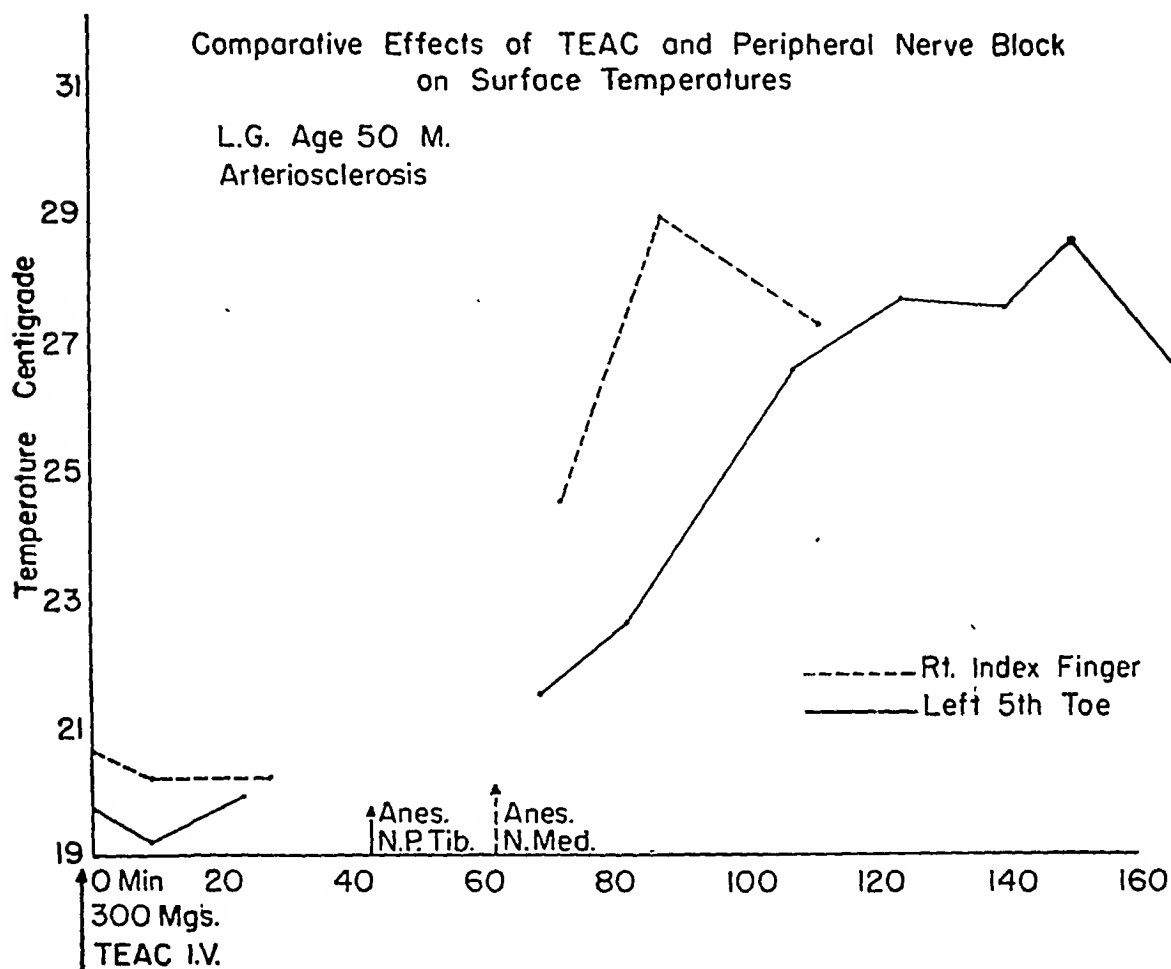


FIG. 5.—Case 5. L. G. Age 50. M.  
Mild diabetic. Claudication both legs after walking  $1\frac{1}{2}$  level blocks, 4 months.  
*Examination:* All pulses +++. Angiospastic claudication.  
After tetraethyl ammonium chloride no rise of temperature in finger or toe. After block, finger temperature rose to  $28.9^{\circ}$  C., the toe to  $28.5^{\circ}$  C. Mild vasoconstrictor recession in finger and toe. Other digits had more recession. (See table, Fig. 6).

measured after vasoconstrictor paralysis was produced by procaine block of mixed peripheral nerves, in two by subarachnoid block.

Tetraethyl ammonium chloride produced significant rises in surface temperature to  $26^{\circ}$  C. or over in only three of 42 extremities (excluding the sympathectomized extremities). Rise of temperature to  $26^{\circ}$  C. or over was obtained in 25 of the 32 extremities subjected to procaine block; rises to  $28^{\circ}$  C. or over in 20 of these extremities; and rises to  $30^{\circ}$  C. or over in 14 of these

TABLE I.—*Summary—All Cases*

Case No.	Initial	Age	Sex	Mg. Teac. I.V.	Extremity	Surface Temperature After Exposure		Maximum Surface Temperature			
						Lowest	Highest	After Teac.		After Block	
								Lowest	Highest	Lowest	Highest
1	F.Z.	52	M	500	Right upper	19.1	19.4	20.3	20.7		
					Left upper	19.1	20.1	19.9	20.4		
					Right lower	19.9	20.5	21.6	26.3	30.2	31.5
					Left lower	20.1	20.6	21.3	25.5	31.5	32.0
2	F.M.	68	M	500	Right upper	19.9	20.9	20.9	21.0	30.4	30.7
					Left upper	19.9	20.4	20.5	21.0	30.7	30.9
					Right lower	20.8	21.7	21.8	25.3	29.8	30.4
					Left lower	21.2	21.8	23.8	25.3	29.2	30.8
3	G.A.	62	M	300	Right upper	21.0	22.5	21.3	22.8	31.0	31.3
					Left upper	21.5	24.0	20.8	23.7	30.0	31.2
					Right lower	19.5	20.0	19.9	20.6	24.0	30.3
					Left lower	20.0	20.5	20.0	20.5	26.6	30.3
4	A.L.	69	M	500	Right upper	19.7	20.4	27.7	29.3	31.1	32.3
					Left upper	20.8	21.3	23.8	29.3	31.8	32.2
					Right lower	20.6	21.3	21.2	22.2	29.9	31.1
					Left lower	21.1	25.2	22.2	25.6	26.2	27.5
5	L.G.	50	M	300	Right upper	20.5	21.5	20.2	21.2	28.7	28.9
					Left upper	19.8	20.5	19.9	20.9	28.7	29.1*
					Right lower	19.4	19.6	19.2	19.5	21.8	26.8
					Left lower	19.5	19.7	19.8	20.0	26.6	28.7
6	N.A.	58	F	500	Right upper	21.0	21.4	21.7	22.3	27.7	28.5
					Left upper	21.2	21.9	21.8	22.5	28.5	28.6
					Right lower	22.9	24.2	23.8	24.8	25.0	26.0
					Left lower	22.6	22.8	22.5	23.0	23.5	24.5
7	C.R.	62	M	500	Right upper	21.2	21.6	22.7	25.6		
					Left upper	21.2	22.2	21.2	22.4	28.8	30.2
					Right lower	22.6	26.1	21.9	24.6	22.4	23.8
					Left lower	23.4	24.1	21.4	22.4	21.7	24.2
8	D.L.	55	M	500	Right upper	20.0	22.0	21.0	21.7	25.0	27.2
					Left upper	20.0	21.2	21.1	23.1	27.9	29.5
					Right lower	20.3	21.0	21.2	21.7	21.0	21.4
					Left lower	20.5	21.0	21.0	21.5	20.8	26.5
9	L.R.	65	M	300 +	Right upper	20.0	21.5	21.0	24.1		
				200	Left upper	20.5	22.0	21.2	23.2		
					Right lower	23.1	23.6	23.3	23.7	22.1†	22.4†
					Left lower	20.6	21.1	20.4	22.1	21.9†	24.0†
10	M.T.†	56	M	200	Right upper	20.4	21.4	20.6	21.6	21.1*	21.6*
					Left upper	19.9	20.4	20.5	20.7	21.0	22.3
11	H.N.	64	M	410	Right upper	21.6	22.8	21.7	22.0		
					Left upper	22.1	22.7	20.8	21.4		
					Right lower**	27.6	30.0	24.6	29.5		
					Left lower**	23.3	28.9	23.1*	28.5*		
12	J.R.	61	M	400	Right upper	20.3	20.5	22.3	23.2		
					Left upper	20.9	21.7	24.7	25.2		
					Right lower**	23.3	28.0	24.5	29.0		
					Left lower**	25.8	29.6	26.3	30.4		

\* Temperature still rising very slowly.

\*\* Sympathectomized.

† Subarachnoid block.

‡ Both legs amputated for arteriosclerotic gangrene.

# Comparative Effects of TEAC and Peripheral Nerve Block on Surface Temperatures

L. G. Age 50 M.

Arteriosclerosis

## Upper Extremities

	After 90" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.5	20.5	21.2	20.9	28.7	29.1*
2	20.6	20.0	20.2	20.2	28.9	29.9*
3	20.6	20.0	20.4	20.1	28.7	28.7*
4	20.6	19.9	20.5	20.0		
5	20.5	19.8	20.4	19.9		
Palm	25.0	24.0	23.8	23.2		
Dorsum	24.6	23.6	23.1	23.0		
Wrist	26.0	26.4	25.1	24.7		
Midforearm	28.8	28.2	28.1	28.0		
Below Elbow	29.5	29.4	29.1	29.6		

## Lower Extremities

	After 90" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	19.6	19.7	19.4	20.0	21.8	27.1
2	19.5	19.6	19.3	19.9	23.3	26.6
3	19.4	19.5	19.2	19.9*	25.1	27.1
4	19.5	19.5	19.2	19.8*	25.2	27.0
5	19.5	19.7	19.5	19.9*	26.8	28.7
Sole	22.2	22.3	21.2	21.5	25.4	27.5
Heel	21.4	21.8	21.4	21.5	26.8	27.8
Ankle	23.7	23.7	22.6	23.6		
Midleg	25.7	24.7	24.7	24.0		
Below Knee	25.2	24.2	25.2	24.5		
Above Knee	26.5	27.1	26.2	25.9		

FIG. 6.—Case 5. L. G. Age 50. M.

After tetraethyl ammonium chloride there were no significant rises of temperature in any of the 4 extremities.

After block, the upper extremity digits rose to from 28.7° C. to 29.1° C., indicating a mild vasoconstrictor recession. The lower extremity digits rose only to from 21.7° C. to 25.2° C. on the right, and from 26.6° C. to 27.1° C. on the left, indicating a moderate to severe vasoconstrictor recession due to occlusive arterial disease.

If tetraethyl ammonium alone were used a high subnormal vasoconstrictor element would have been overlooked in the upper extremities and a moderate vasoconstrictor element would have been overlooked in the left lower extremity.

# Comparative Effects of TEAC and Peripheral Nerve Block on Surface Temperatures

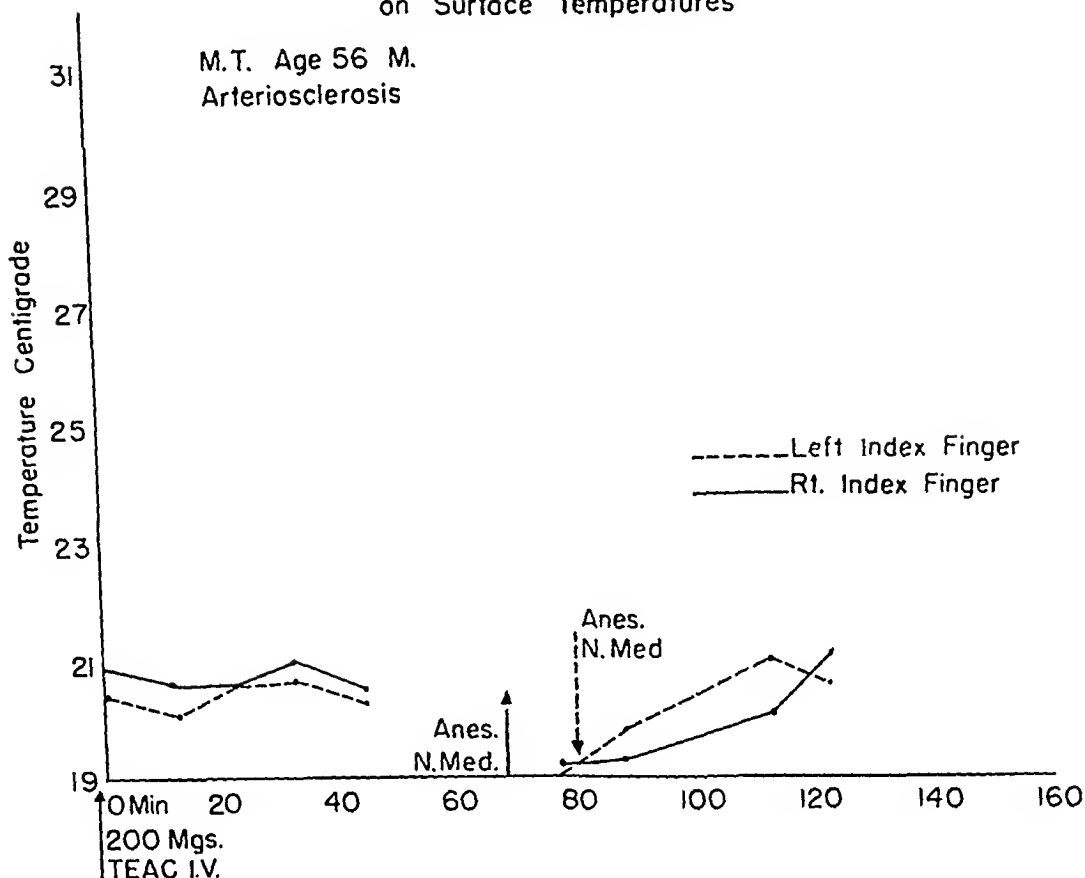


FIG. 7.—Case 10. M. T. Age 56. M. Extensive general and peripheral sclerosis. Amputations through both low thighs for arteriosclerotic gangrene in 1939 and 1941. Examination: Gangrene of the right ring and left middle fingers, 4 months. Marked cyanosis and pallor of both hands. Both brachial pulses + + +, radials and ulnars not felt. X-rays show mild calcification of the right subclavian artery; none in the hands, forearms or arms. Old valvular heart disease. Surface temperatures both after tetraethyl ammonium chloride and after block show practical absence of vasoconstrictor tone.

## Comparative Effects of TEAC and Peripheral Nerve Block on Surface Temperatures

M.T. Age 56 M. Arteriosclerosis

### Upper Extremities

	After 70" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.4	20.4	21.6	20.7	22.1*	22.3
2	20.9	20.4	21.0	20.7	21.1*	21.0
3	20.4	20.4	21.0	20.6	21.6*	21.1
4	20.4	19.9	21.1	20.6		
5	20.4	19.9	20.6	20.5		
Palm	24.4	24.9	23.7	24.3		
Dorsum	22.9	24.4	23.6	23.8		
Wrist	25.4	24.9	25.0	25.0		
Midforearm	27.9	26.9	27.5	26.8		
Below Elbow	28.9	27.9	28.6	28.0		
Above Elbow	29.9	29.4	29.4	28.9		

FIG. 8.—Case 10. M. T. Age 56. M. Neither tetraethyl ammonium chloride nor block produced significant rises of temperature. The vasoconstrictor element has practically completely disappeared. On the right side, after block, readings were discontinued before actual maxima were reached. The slow rise after 35 minutes, however, indicates that the figures are close to the maxima. Although tetraethyl ammonium and block produced the same results, no rise of temperature was possible and the similarity of responses is no proof of the dependability of tetraethyl ammonium chloride.

extremities. In all three of the extremities which showed rises to  $26^{\circ}$  C. or over by tetraethyl ammonium chloride, nerve block produced a rise of temperature above the normal level of  $30.5^{\circ}$  C. In the sympathectomized extremities the drug was followed by a change of from  $-1.7^{\circ}$  C. to  $+1.2^{\circ}$  C. When vasodilatation occurs as the result of tetraethyl ammonium chloride, the average duration of a satisfactory effect ( $25^{\circ}$  C. or over) is 15 minutes.

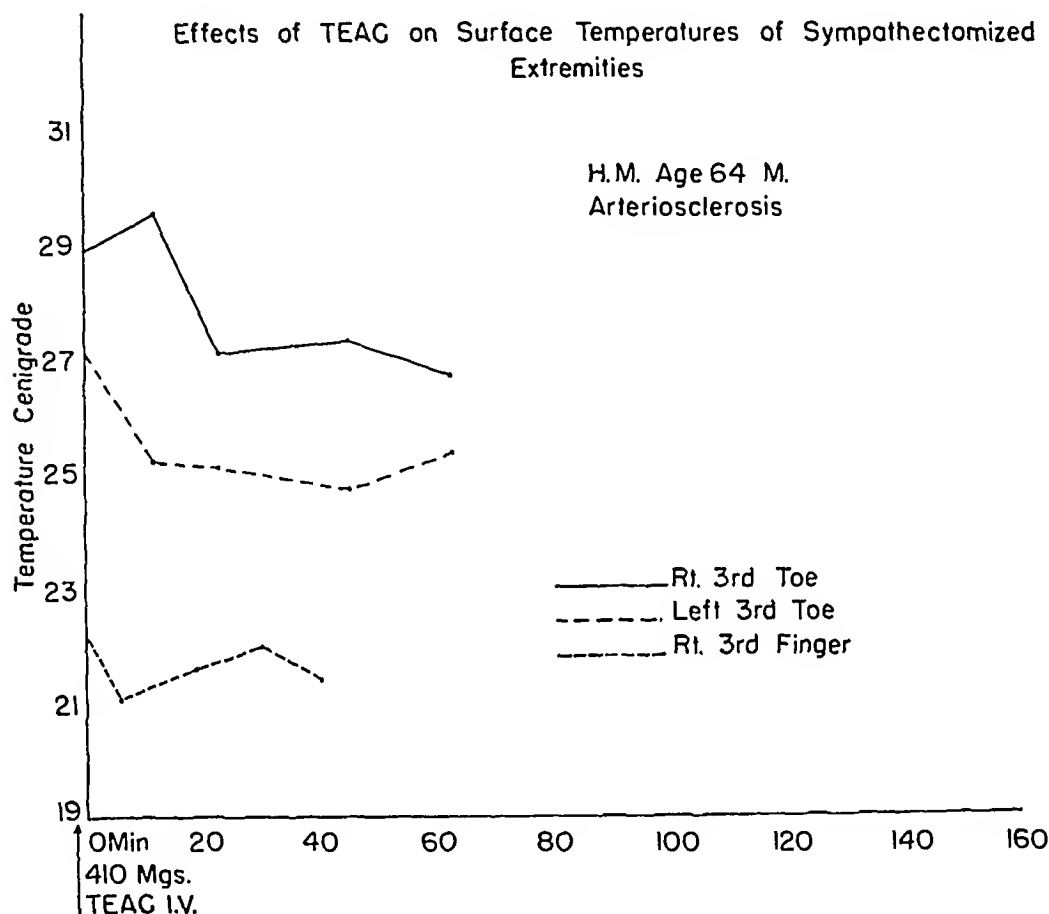


FIG. 9.—Case 11. H. M. Age 64. M.  
Claudication of both calves after walking two blocks since October, 1944; night pain in the soles since November, 1944.  
*Examination:* Femoral pulses ++, all others 0. Bilateral marked elevation ischemia, slight dependent rubor. Moderate vasoconstrictor element. Bilateral lumbar ganglionectomy, March, 1945.  
After tetraethyl ammonium chloride, the right toe showed a  $0.6^{\circ}$  C. rise of temperature; the left showed a  $1.7^{\circ}$  C. fall of temperature.  $0.6^{\circ}$  C. is within the limit of error in the experiment. The finger showed no significant change.

#### CONCLUSIONS

I. Comparison of tetraethyl ammonium chloride given intravenously, and of vasoconstrictor paralysis produced by peripheral nerve procaine block, shows that tetraethyl ammonium chloride is undependable and unsatisfactory as a diagnostic agent in estimating the vasoconstrictor element in extremities affected by peripheral arteriosclerosis.

2. In peripheral arteriosclerosis vasodilatation due to tetraethyl ammonium chloride is infrequent; when it occurs it is only partial and its duration is short.
3. These experiments throw grave doubt on the value of tetraethyl ammonium chloride as a practical therapeutic agent in peripheral arteriosclerosis.

## Effect of TEAC on Surface Temperatures of Sympathectomized Extremities

H.M.Age 64 M.					Arteriosclerosis	
Upper Extremities					(not Sympathectomized)	
		After 15" Exposure		Max. After TEAC		
		R	L	R	L	
Digit 1		22.8	22.4	21.9	21.2	
2		22.6	22.3	22.0	21.1	
3		22.1	22.4	22.0	20.8	
4		21.9	22.1	21.7	21.3	
5		21.6	22.7	21.8	21.4	
Palm		24.3	24.6	24.1	23.7	
Dorsum		24.4	25.7	23.1	22.5	
Wrist		26.1	26.1	25.4	25.0	
Midforearm		28.1	28.4	28.1	27.6	
Below Elbow		29.9	29.6	29.4	28.7	
Above Elbow		29.1	29.1		28.7	

Lower Extremities (Sympathectomized)							
		After 15" Exposure		Max. After TEAC		Effect of TEAC	
		R	L	R	L	R	L
Digit 1		27.6	28.5	28.2	28.5*	+0.6	0
2		29.1	28.9	29.2	28.5*	+0.1	-0.4
3		28.9	27.0	29.5	25.3	+0.6	-1.7
4		24.0	23.3	24.6	23.1*	+0.6	-0.2
5		30.0	27.5	28.9	26.2	-1.1	-1.3
Sole		28.5	28.6	27.3	27.7	-1.2	-0.9
Heel		30.1	29.0	28.5	29.6	-1.6	+0.6
Ankle		29.3	30.6	29.2	29.6	-0.1	-1.0
Midleg		28.3	28.0	27.2	27.2	-1.1	-0.8
Below Knee		28.6	26.6	26.6	26.2	-2.0	-0.4
Above Knee		29.1	29.6	31.0	31.0	+1.9	+1.4

FIG. 10.—Case 11. H. M. Age 64. M.

*Upper Extremities:* (Not sympathectomized). After tetraethyl ammonium chloride there was no significant change in surface temperature. In fact, all but the right 5th digit showed an actual fall of temperature.

*Lower Extremities:* (Sympathectomized) After tetraethyl ammonium chloride there were changes in surface temperature varying on the right from  $-2.0^{\circ}$  C. to  $+1.9^{\circ}$  C. and on the left from  $-1.7^{\circ}$  C. to  $+1.4^{\circ}$  C. These changes are not significant. In the digits the rise on the right was not more than  $0.6^{\circ}$  C.; on the left there was a fall in four digits.

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# CHRONIC PROGRESSIVE INFECTIOUS GANGRENE OF THE SKIN\*

A PATIENT WITH EXPOSURE TO COLD WAVE SOLUTION

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CHRONIC INFECTIOUS GANGRENE of the skin is an uncommon disease. Meleney<sup>1</sup> distinguished four varieties: Postoperative progressive bacterial synergistic gangrene, gangrenous impetigo; fusospirochetal gangrene; and amebic infection with gangrene. Occasional cases are seen which do not fit any of these chronic categories. They do not conform with the characteristic pictures of the acute infectious gangrenous lesions of the skin, and they differ in their natural history from the ordinary pyogenic infections of the skin and subcutaneous tissues.

The course of an infection is determined by the virulence of the bacteria, by the nature of the tissue to which they have gained access, and by the ability of the patient's natural defenses to cope with the infection. The individual's inherent ability to combat infection can be modified by a number of different factors, among them, exposure to injurious chemical agents. Exposure to benzol, for instance, causes a leukopenia and renders the patient peculiarly susceptible to infections of the skin and other organs. The patient to be described had an unusual type of chronic progressive gangrene of the skin of the abdominal wall. Her defense reaction was peculiar in that a leukopenia, rather than a leukocytosis, accompanied the infection. Recently, Cotter<sup>2</sup> reported five patients (Table V) who showed skin and systemic manifestations which he attributed to the toxic effects of thioglycolic acid in "cold wave" hairdressing solutions. The patient to be described, a hairdresser, is therefore of particular interest because in addition to the problem of management of a serious surgical lesion, she raises the question of the rôle that exposure to thioglycolic acid or thioglycolates in "cold wave" solutions may have played in her peculiar susceptibility to infection.

## CASE REPORT

The patient was a 33-year-old single hairdresser. In 1934 she had been operated upon for acute appendicitis. The convalescence was complicated by the development of pelvic and perirenal abscesses which required drainage. That same year she was operated upon for symptoms of intestinal obstruction. Bilateral salpingectomy and right oophorectomy were done. Most of the left ovary was also removed for "cystic oöphoritis." She recovered satisfactorily from these operations and had always to watch her diet for fear of gaining weight.

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\* Submitted for publication, February 1948.

The patient worked as a hairdresser for 11½ years in addition to attendance at a hairdressing school for 2 years. For 9 years she had worked in a very active beauty parlor establishment of her own. Since March, 1944, she had been waving hair by the "Cold Wave" method. She worked long hours, often up to 10 or 12 hours a day and administered personally 6 to 12 "cold-wave" treatments a month. She developed no rashes or other obvious signs of toxicity, however, except that her finger tips would become very sore after applying cold wave solutions. She kept on working until her present acute illness.

During the past 2 years she had shown signs of unusual susceptibility to infection. In June, 1945, she was stung by a mosquito on the medial aspect of the right ankle. The lesion became secondarily infected, she was febrile and acutely ill for several days. The lesion took 6 weeks to heal and a brown spot is still visible at the site of the lesion. In January, 1946, she bumped the lateral aspect of her ankle against a rocking chair. There was no obvious break in the skin but an abscess developed there. It had to be "lanced" twice, sulfonamides were administered, and the lesion required 4 weeks to heal. The site of this lesion, too, is still marked by the presence of an area of brown pigmentation.

For 3 months before the onset of her present acute illness, she had begun to complain of easy fatiguability. She had noticed a small external hemorrhoidal tab during that time, but it had caused no inconvenience until April 21, 1947, when she noticed that the hemorrhoid had suddenly increased in size. She felt feverish and was too ill to leave her house. Her family physician was called to see her and for the next 3 days she was treated with bedrest and oral penicillin. She took 400,000 units a day in the form of tablets (50,000 units each). No sulfonamides were administered. She failed to improve and she was admitted to the Jane Brown Memorial Unit of the Rhode Island Hospital on April 24, 1947,\* where penicillin therapy was continued and, in addition, sulfadiazine (1 Gm. every 4 hours orally) was started. Examination of the blood on admission, before any therapy had been started, revealed only 6000 white blood cells per cubic millimeter with 78 per cent polymorphonuclear cells and 21 per cent lymphocytes. A leukocytosis had been anticipated and, because of its absence, the sulfadiazine was discontinued for fear of aggravating a leukopenia.

Upon admission to the hospital, physical examination had revealed a large gangrenous external hemorrhoid and a blister-like pustule on the lower third of her left leg. This contained thin cloudy fluid. Nothing grew from it on culture. Subsequently, she developed a similar blister in the lower end of a broad right paramedian lower abdominal scar. Both blisters broke spontaneously. The one on the shin healed; that in the abdominal scar left an ulceration which spread progressively, instead of healing, until the surface of the entire scar had "melted away."

The oral temperature on admission was 104° Fahrenheit. During her hospital stay the temperature varied between 102 and 104 orally. The thrombosed hemorrhoid gradually separated and by the end of 3 weeks it was no longer present. Her general condition continued to fail, however. The lateral abdominal scar also became ulcerated and induration developed in the skin between the scars. She had severe night sweats and continued to lose weight. An exploratory laparotomy under ether anesthesia and through a subcostal incision was done on May 21, 1947. Abdominal Hodgkins disease or a liver abscess had been suspected. Neither was found. The wound healed well and the operation appeared to have had no adverse effect. She lost 23 pounds in weight during the first 5 weeks of hospitalization.

Among the numerous laboratory examinations done (Tables I and II) only 2 were of positive interest, namely, the increased sedimentation rate and the leukopenia without agranulocytosis.

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\* The writers are indebted to Dr. William P. D'Ugo and to Dr. Daniel V. Troppoli for much of the information relative to this hospital admission.

On May 29, 1947, she was transferred from the Jane Brown Memorial Unit of the Rhode Island Hospital to the Baker Memorial division of the Massachusetts General Hospital. She appeared critically ill and had an oral temperature of 101 degrees Fahrenheit with a pulse rate of 120 beats per minute. Her blood pressure was 120 millimeters of mercury systolic and 68 diastolic, but her skin was cold and clammy. Except for the general systemic reaction, the positive findings were confined essentially to the right lower quadrant of the abdomen. Here there were 2 operative scars, a paramedian one and an

TABLE I.—*Blood Cytology from Records of Jane Brown Memorial Unit of the Rhode Island Hospital*

Date (1947)	Red Blood Cells Per Cubic Millimeter of Blood	Hemoglobin (Gm. Per Cent)	White Blood Cells Per Cubic Millimeter of Blood	Differential Count (As Per Cent of Total White Blood Cells)				
				Polymorpho- nuclear Cells	Lympho- cytes	Mono- cytes	Baso- philes	Eosino- philes
24 April	2,640,000	....	6,000	79	21	..	..	..
26 April	.....	....	6,200	71	27	1	..	..
28 April	.....	....	7,850	57	42	1	..	..
30 April	3,690,000	10.8	4,550	66	32	2	..	..
3 May	.....	....	3,750	61	37	2	..	..
5 May	.....	....	2,900	57	43	..	..	..
10 May	.....	....	2,550	62	38	..	..	..
11 May	.....	....	1,750	..	..	..	..	..
14 May	.....	....	4,600	59	41	..	..	..
22 May	3,890,000	11.2	3,650	77	23	..	..	..
26 May	.....	....	9,350	80	17	1	..	..

TABLE II.—*Additional Laboratory Data from Records of Jane Brown Memorial Unit of the Rhode Island Hospital.*

Date (1947)	Examination	Result	Other Tests Performed (April–May 1947)	
			Examination	Result
25 April	Hinton	Negative	Typhoid-dysentery agglutina- tions	Negative
1 May	Hinton	Negative	Heterophile antigen (5 tests)	Negative
24 April	Blood culture	Sterile	Skin tests and opsonocytophagic test for brucellosis	Negative
30 April	Blood culture	Sterile	Tuberculin test 1:1000	Negative
16 May	Blood culture	Sterile	Frei test	Negative
17 May	Blood culture	Sterile	Roentgenogram of chest	Negative
			Plain roentgenogram of abdomen	Negative
			Sedimentation rate (4 tests)	All elevated to 3 times normal
			Icteric index	Normal
			Stools	Negative for ova, parasites and blood
			Smears for malaria (2 tests)	Negative
			Excretion of phenolsulfon- phthalein	Normal
			Urinalysis and culture of urine	Negative

oblique one more laterally (Fig. 1). Both were now open ulcerations throughout most of their extents since the covering epithelium had undergone a dissolution. There was no undermining of the skin. Around and between the two lower abdominal ulcerated scars the skin was indurated and edematous. Nodular elevations about 0.5 cm. in diameter in the skin suggested multiple abscesses but there was no fluctuation. Immediately around the outer of the two scars, and extending mostly laterally from it was an irregular swell-

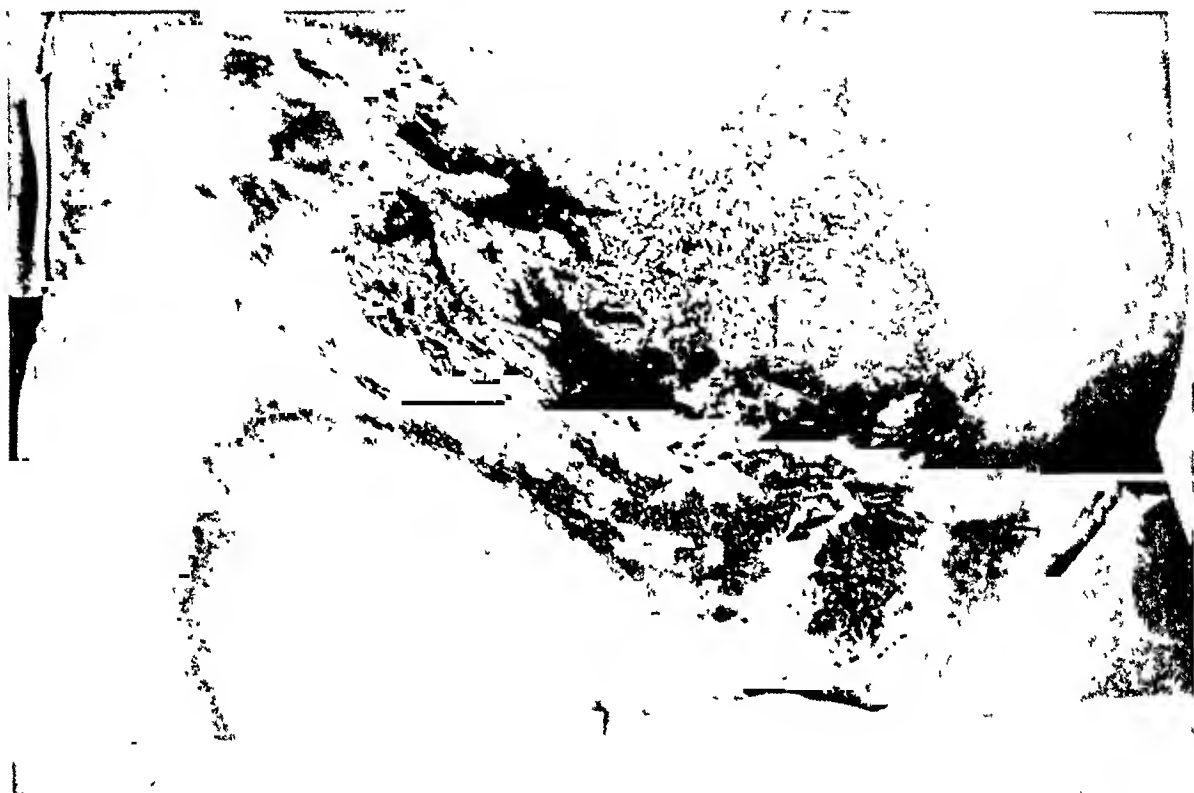


FIG. 1.—Photograph of lesion of abdominal wall before operation. Note the dissolution of epithelium over the scars from previous operations, the margin of cellulitis extending from the lesion particularly upward and to the right, and the granulomatous appearance of the lesion with blister formation.



FIG. 2.—Photograph taken on June 21, 1947, at the time of the second dressing to show the extent of the excision. The area is granulating well and some of the Thiersch grafts have taken.

ing measuring 6 by 9 centimeters. The swelling was nodular. The nodules measured 0.5 to 1.0 cm. in diameter and some were ulcerated. No pus could be obtained from any of the ulcerated nodules. A culture from one of the ulcerated areas showed *E. coli*, *Staphylococcus aureus* and alpha-hemolytic Streptococci. Cultures for fungi were negative. On the inferior lateral surface of the granulomatous tumor, the surface epithelium was raised as a bleb by cloudy fluid. This fluid was examined for fungi and yeasts but none was found. The smear did show many polymorphonuclear cells and a few gram-positive cocci. During 5 days of observation, the granulomatous lesion increased in size, extending

TABLE III.—*Blood Cytology from Records of Massachusetts General Hospital.*

Date (1947)	Hemo- globin (Gm. Per Cent)	White Blood Cells Per Cubic Millimeter of Blood	Polyomor- phonu- clear Cells	Differential Count (As Per Cent of Total White Blood Cells)					Platelets	
				Large Lymph- ocytes	Small Lymph- ocytes	Mono- cytes	Baso- philes	Eosino- philes		
29 May	10.7	7,700	74	..	24	2	..	..	Slightly	increased
3 June	....	6,400								
4 June*	12.0	4,200	86	..	11	1	..	1	Slightly	increased
5 June	....	2,700								
5 June	....	3,300	54	3	40	3	..	..	Slightly	increased
6 June	....	4,300	64	1	32	1	..	2	Normal	
7 June	....	5,000	62	2	30	5	..	1	Normal	
9 June	13.4	6,700	75	..	22	3	..	..	Normal	
10 June	12.6	9,800	87	..	10	1	..	2	Normal	
11 June	12.6	6,000	72	2	20	6	..	..	Normal	
12 June	11.4	6,600	73	..	24	2	..	1	Normal	
13 June	....	5,800	63	..	32	4	..	1	Normal	
14 June**	....	3,800	75	..	20	2	..	2	Slightly	increased
16 June	....	4,700	61	..	32	5	..	2	Slightly	increased
18 June	12.2	4,000	50	..	47	3	..	..	Norma.	
19 June	....	5,400	53	5	35	5	1	1	Slightly	increased
20 June	11.8	4,600	54	..	40	6	..	..	Slightly	increased
21 June	12.6	5,400	49	11	38	..	..	2	Slightly	increased
23 June	....	6,700	78	..	18	2	..	2	Slightly	increased
24 June	....	3,900	52	1	44	2	..	1	Increased	
25 June	....	6,900	71	..	27	..	..	2	Increased	
26 June	....	5,600	69	..	30	1	..	..	Slightly	increased
27 June	....	6,400	63	..	33	3	..	1	Increased	
28 June	....	5,600	55	2	41	2	..	..	Normal	
30 June	10.7	6,300	58	..	38	2	..	2	Slightly	increased
8 July	10.2	3,400								
11 July**	....	7,300	41	4	52	..	..	2	Normal	
12 July	....	....	61	1	34	3	..	1	Normal	
15 July	12.2	7,500	58	..	38	1	..	3	Normal	
21 July	12.2	7,400	53	1	43	2	..	1	Normal	
1 August***	11.8	6,800	49	..	46	2	1	2	Normal	

\* One per cent of cells in this smear unclassified.

\*\* One "blast" form seen in white cell differential in this smear.

\*\*\* At this examination, the red blood cell count was 3.84 million; the hematocrit was 40%.

laterally for the most part and the ulceration on the paramedian scar spread in all directions. It extended onto the pubis to 1 centimeter from the vulva. The entire involved area was circumscribed in the right lower quadrant of the abdomen by a one-half inch margin of bluish-purple discoloration (Fig. 1).

The admission white blood cell count was 7,700 per cubic millimeter of blood with 74 per cent polymorphonuclear cells. The hemoglobin concentration was 10.7 Gm. per cent. This rose to 12.0 Gm. per cent after the transfusion of 1500 cc. of citrated blood. The blood cytology throughout her hospital stay was characterized by a variable degree of

leukopenia, a normal or slightly augmented proportion of platelets in the smear, and occasionally a relative lymphocytosis (Table III). Examinations of the urine showed only a few white blood cells in the centrifuged specimens and 1+ albumen which was not found in a catheter specimen. Examinations of the stool on 5 occasions were negative for blood, parasites and ova. One specimen was cultured and no pathogens were found. The heterophile antigen test was negative and agglutination tests for brucellosis\* and for the typhoid-dysentery group were negative. Two blood cultures were negative. The patient's blood was Rh positive and belonged to Group O. Other tests that were done are recorded in Table IV.

### RECORD OF TEMPERATURE AND PULSE RATE

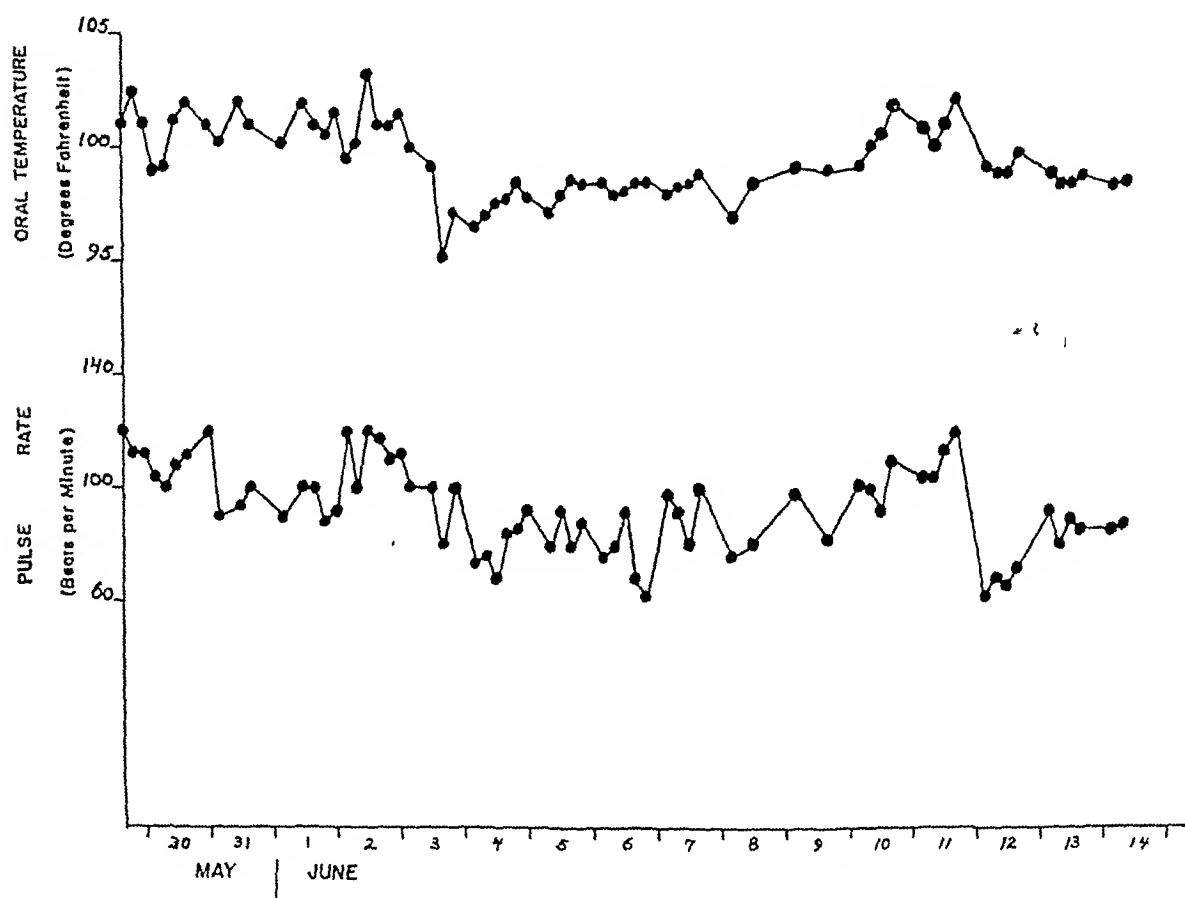


FIG. 3.—A chart of the patient's temperature and pulse rate before and after excision of the lesion on June 3, 1947. Note the drop of the temperature to subnormal levels for the day of operation and for the next day.

On June 3, 1947, a block-excision of the involved skin of the right lower quadrant was done by diathermy under ether anesthesia. The excision was carried through the subcutaneous tissue and onto the deep fascia which did not appear involved. The circumference of the excision was carried beyond the band of bluish-purple discoloration (Fig. 2). The inflammatory process included multiple small areas of necrosis in the subcutaneous tissue. There was no gross evidence of actinomycosis and cultures from the necrotic areas showed non-hemolytic *Staphylococcus aureus* and alpha-hemolytic *Streptococcus*. Anaerobic cultures showed no growth. The *Staphylococcus* grew in a medium containing 0.3 units of penicillin per cc., but was inhibited by 0.6 units per cc. The *Streptococcus* grew even when the medium contained as much as 5 units of penicillin per cc.

\* Opsonocytaphagic index and skin tests for brucellosis were done at the Jane Brown Memorial Unit of the Rhode Island Hospital and were negative.

The effect of the excision of the lesion upon the patient's temperature was remarkable (Fig. 3). Beginning six days after the excision and twice again during the next month, "postage-stamp" split-thickness skin grafts from the thighs were applied to the granulating surface until it was almost completely covered. There was a temperature reaction after the first graft, but none after the others. A specimen of sternal marrow was taken for biopsy on July 31, 1947. Supra vital stains of impressions from the marrow as well as histologic sections of it showed scant marrow with no diagnostic abnormality. (Since this paper was written the patient has been hospitalized again because of severe anemia and leukopenia following an upper respiratory infection and a paronychia. At this admission, blood smears showed severe depression of the platelet count and two bone marrow aspirations showed "insufficient tissue for diagnosis" and "fibrosis of bone marrow" respectively.)

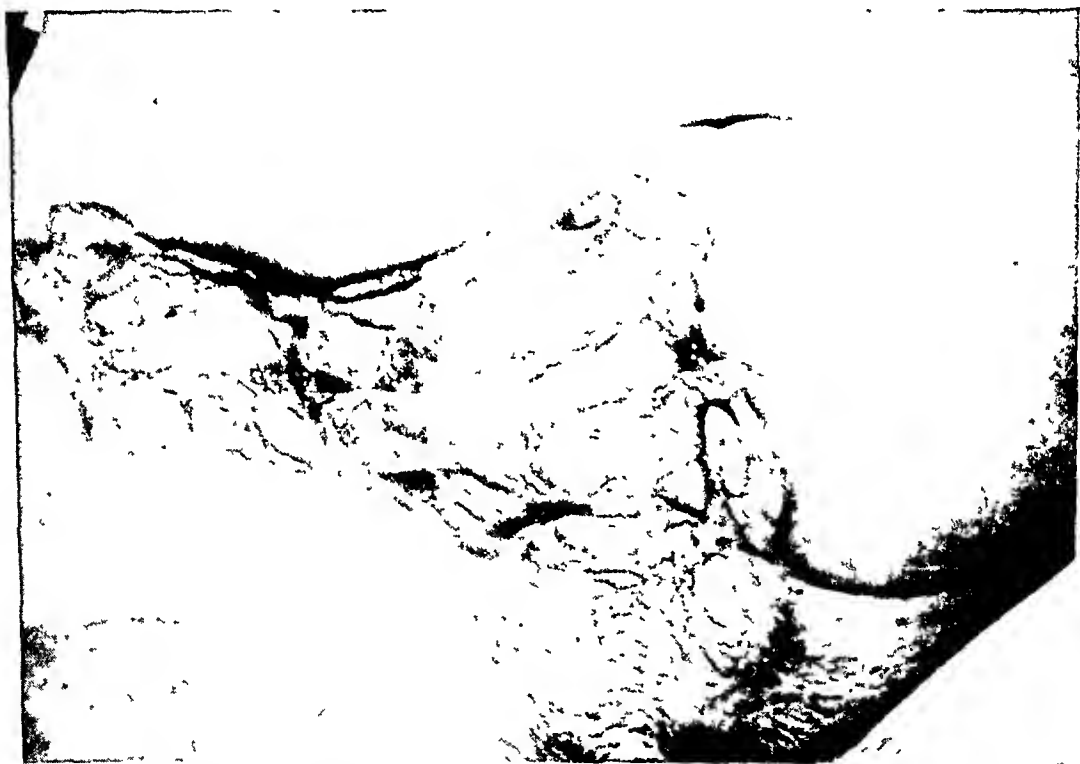


FIG. 4.—Appearance of grafted area on July 30, 1947, eight weeks after excision of the lesion.

She did very well after excision of the infected skin. The grafts grew satisfactorily and by the time she left the hospital, the area had epithelialized almost completely (Fig 4). On the day of discharge, August 2, 1947, she weighed 140.5 pounds.

#### Follow-Up Notes

*October 21, 1947:* The patient has gained weight so that she now weighs 152 pounds in her dress and shoes. The right lower quadrant of the abdomen is completely epithelialized (Fig. 5) and depressions in the grafted area are filling out. The concentration of plasma proteins is 6.0 grams per cent. The hematocrit is 36 per cent (hemoglobin 12.2 Gm. per cent). A count of the white blood cells was not done. She was encouraged to lose weight and a well balanced low-caloric diet was prescribed

## GANGRENE OF THE SKIN

December 18, 1947: The patient had a pharyngitis two weeks ago which subsided on penicillin by mouth. She has had slight ankle edema and there is a little brownish discoloration of the skin of the ankles medially on both sides, suggesting old phlebitis in the deep femoral system of veins. The hemoglobin concentration is 70 per cent (Sahli). The white blood cell count is 7,000 cells per cubic millimeter. The differential count is: 60 per cent polymorphonuclear cells; 37 per cent lymphocytes; 2 per cent monocytes; and 1 per cent basophiles. Her weight is 152 pounds. She has been unable to stay on her diet, but promises to make a greater effort to do so.

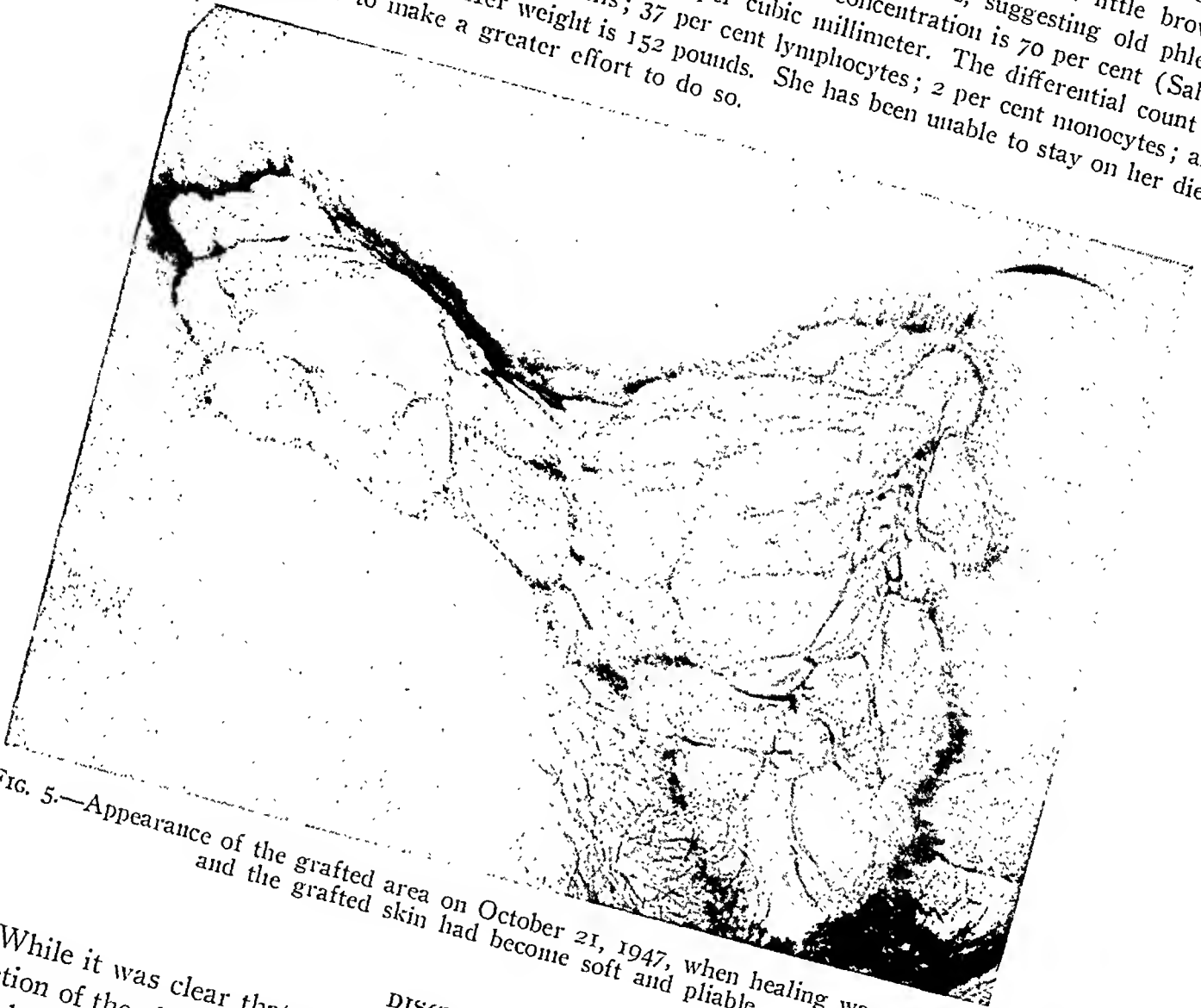


FIG. 5.—Appearance of the grafted area on October 21, 1947, when healing was complete and the grafted skin had become soft and pliable.

### DISCUSSION

While it was clear that the principal cause of this patient's illness was the infection of the abdominal wall, the nature of the lesion was obscure. It was a granulomatous infection of the skin and subcutaneous tissue causing ulceration of the skin with blister formation and dissolution of epithelium over abdominal scars and in patchy areas over the infected skin. There was no tendency to form a solitary encapsulated abscess. It had not responded to penicillin and to streptomycin therapy. Because of the leukopenia, a trial of sulfonamide therapy was not made. Activated zinc peroxide had been used at the Jane Brown Memorial Unit of the Rhode Island Hospital on the ulcerated surfaces, but the lesion spread despite it. The opinion of the consulting dermatologist was that the gross appearance of the lesion resembled most closely actinomycosis of the skin or a coccidioides infection.



The lesion was treated as recommended by Meleney<sup>1</sup> for postoperative progressive bacterial synergistic gangrene. The skin of the right lower quadrant of the abdomen was excised beyond the inflammatory margin. Penicillin ointment was used in the dressing instead of activated zinc peroxide. Pathologic examination of the specimen was reported as follows:

*"Abdominal Wall.* The specimen consists of a large irregular segment of skin from the lower abdominal wall, measuring 20 x 16 centimeters with attached subcutaneous fat. There is irregular gray-red ulceration in scattered areas. In other areas there is a peculiar firm nodularity in the surface of cobblestone-like structure. In the outer portion of the specimen is an area in which the epidermis is lifted from the underlying tissue by thin purulent material. On section, several places show a firm fibrous thickening, others a

TABLE IV.—*Additional Laboratory Data from Studies done at Massachusetts General Hospital.*

Date (1947)	Examinations of the Blood												Cephalin Flocculation	
	*Liver Func- tion (as reten- tion)	Non- Pro- tein (Nitro- gen per cent)	Plasma Pro- tein (Gm. per cent)	Albu- min Glob- ulin Ratio	Chlo- rides (milli- equiv- alents per liter)	Vanden- berg Reaction	Prothrombin Time (seconds)	Nor- mal		Cho- les- terol (mg. per cent)	Phos- phorus (mg. per cent)	Alka- line Phos- phatase (units per cent)		
							Test Speci- men	15	189	...	4.8	5.2	Negative	After 24 Hrs.
29 May	..	19	6.4	....	95	Normal								
1 June	..	..	....	....	..	.....	18	15	189	...	...		Negative	2+
2 June	22													
21 June	..	..	....	....	..	.....	..	..	...	...	...		Negative	1+
23 June	..	..	....	....	..	.....	..	..	...	4.8	5.2			
24 June	..	24	5.79	1.74	.	Normal	..	..	...	...	...		Negative	1+
25 June	..	..	....	....	..	.....	19	17						
27 June	6													
21 July	..	26	5.92	1.82										
22 July	4													

\* Five milligrams of bromsulphalein are injected intravenously per kg. of body weight and the amount remaining in the circulation is determined 45 minutes after injection.

purulent necrosis of the upper layers. *Note:* There is no evidence of fungus infection histologically. *Diagnosis:* 'Acute and chronic inflammation with ulceration and necrosis.'

The drop in the patient's temperature immediately postoperatively, and the steady improvement in her general condition were remarkable. Nevertheless, in spite of folic acid, ferrous sulphate and crude liver extract, the hemoglobin concentration of the blood by the time she left the hospital was only 11.8 Gm. per cent. An examination of the sternal bone marrow shortly before she was discharged showed no recognizable abnormality. The fluctuating leukopenia, without a frank agranulocytosis, was difficult to explain. It was certainly not related to the administration of penicillin and while penicillin

sensitivity tests against the principal offending organisms showed that the drug was not especially effective against those organisms, the drug was used nevertheless after operation to control secondary invaders in the open lesion during the multiple-stage skin grafting.

It was suspected that the peculiar hematologic response that this patient exhibited to infection and, in addition, the presence of impaired liver function (Table IV), could be due to an intoxication. Her history was carefully searched for possible exposure to noxious agents. The only possibility that could be disclosed was that she might have been exposed to some injurious agents in connection with her work as a hairdresser. Careful questioning revealed no possibility of exposure to carbon tetrachloride or to benzol outside

TABLE V.—*Tabulation of Five Patients Reported by Cotter.<sup>2</sup>*

Case No.	Skin Lesions	Anemia	Leukopenia	Cephalin Flocculation Test	Comment
1	Present. ? X-ray dermatitis.	Hemoglobin 13 Gm. per cent.	None	Positive	Serum phosphatase normal. Recovered 6 months later.
2	Present. Pustules in scalp.	Told she had anemia.	Slight	Strongly positive	Improved thrss months later.
3	Burning and itching of skin strongly positive patch test.	Hemoglobin concentration low.	Granulopenia	Positive	Cephalin flocculation test negative after 3 months.
4	Diffuse itching rash. Patch test positive.	Hemoglobin 10 Gm. per cent. Red blood cell count 3,200,000 per cu. mm.	White blood cell count 3000 per cubic millimeter. Low granulocyte count.	.....	Serum phosphatase 6.1 Bodansky units per cent. Made complete recovery.
5	Slight skin rash. Pustular eruption around roots of hair.	Hemoglobin 10.6 Gm. per cent. Red blood cell count 3.6 million.	White blood cell count 4,600 per cu. mm. Later 4,400 with low granulocyte count.	Positive	Platelets recorded as "scanty" in blood smear. Improved and then had a relapse after her fifth cold wave. No improvement during next 2 months.

of her work. The patient then submitted for examination samples of all the materials and solutions that she has used in her beauty parlor. These were examined by the Division of Occupational Hygiene, Massachusetts Department of Labor and Industries. None of the solutions tested contained benzol or other known toxic agents except for the known presence of thioglycolic acid and/or thioglycolates in cold wave solutions.

The active ingredient in cold wave solutions has already been suspected of exerting toxic effects in man. Cotter<sup>2</sup> has reported cases with leukopenia and liver damage (Table V) which he attributed to intoxication from the active ingredients of cold wave solution. Hardy<sup>3</sup> found leukopenia in two workers engaged in making cold wave solutions. A vacation in both cases resulted in a return of the white blood cell count to normal.

McCord and his associates<sup>1, 5</sup> have made an extensive laboratory study of thioglycolic acid and thioglycolates in different concentrations. They could detect no abnormalities attributable to repeated injections of sodium thioglycolate (3.58 per cent; pH 8.6) into rats and rabbits. With sodium thioglycolate in a cream preparation (7.3 per cent thioglycolate), positive skin patch tests were obtained in 8 per cent of 182 subjects exposed for 24 hours and in seven of 12 subjects exposed for 96 hours. Thioglycolic acid, however, produced positive patch tests even when the exposure of the skin to a 4.6 per cent solution was only for four to six hours.

These workers report that both single and repeated subcutaneous injections of thioglycolic acid produced skin ulcerations which were very slow to heal. Repeated injections, even in small doses, also led to minor changes in the kidney and to more severe changes in the liver. These were interpreted as being reversible. No significant changes were detected in the cytologic examinations of the blood except for a "slight increase in the platelet count." There may have been some lymphocytosis. While pointing out that the condemnation of all cold wave process solutions is not warranted, McCord<sup>5, 6</sup> does state the need for protection of professional beauty shop operators who are exposed to thioglycolates and other cosmetic chemicals. With reference to injections of sodium thioglycolate, it is interesting to note that Brunschwig and his associates<sup>7, 8</sup> found that repeated injections of this compound and certain other sulfhydryl compounds exerted a protective action against the injurious effects of chloroform and carbon tetrachloride upon the liver in dogs and in rats.

It is important to emphasize that it would be hazardous to state categorically that the patient described above owed her peculiar hemocytologic response to infection and the evidence of liver impairment to thioglycolic acid or thioglycolate intoxication. The evidence is purely circumstantial. It is fair to state, however, that as far as intoxications are concerned, this patient had no exposure to any other of the known industrial poisons and none of these could be detected in the solutions with which she worked. The proportion of free thioglycolic acid to its neutralized salt in the solutions with which she has worked cannot be told with any degree of certainty. Nevertheless, from the point of view of occupational medicine, it was thought important to present this case because of the increasing interest in the problem, and because, with accumulation of data from different sources it may be possible to indict or to exonerate cold wave solutions from responsibility in cases such as this "beyond a reasonable doubt."

#### CONCLUSIONS

1. An unusual case of chronic progressive infectious gangrene of the skin is described.
2. The possible relationship between the manifestations of the infection and exposure to thioglycolic acid and/or thioglycolates in "cold wave" solutions is discussed.

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# A STUDY OF THE BETA 17 KETO-STEROIDS IN A CASE OF PSEUDO-HERMAPHRODITISM DUE TO ADRENAL CORTICAL TUMOR\*

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EVIDENCE WHICH ATTESTS THE VALUE of determining the beta 17 keto-steroids in the urine when confronted with the necessity of making a diagnosis of the cause of abnormal sexual development is constantly accumulating. The beta 17 keto-steroids as studied in the urine of this one-year-old girl with a masculinizing syndrome conform well to the pattern that has been evolving in this condition. This case is reported for the purpose of adding further confirmatory evidence to the importance of making these determinations.

The keto-steroids have been used as indicators because of the information they convey about the activity of the adrenals. Of all the steroids found in the adrenal gland those which have a keto group on carbon 3, are the ones which possess adrenal cortical function. Thus the interest in so-called keto-steroids. When interest is narrowed down to the adrenal keto-steroids that have action on sexual characteristics, attention is focused on the 17 keto-steroids. The 17 keto-steroids are those with a distinctive side chain on carbon 17. Recently, a further refinement in diagnosis has taken place. The 17 keto-steroids have been divided into alpha and beta fractions and data has been collected upon the relative importance of the beta fraction. When the beta fraction is in pronounced excess, the patient will have an adrenal cortical adenoma or carcinoma. This has been the uniform finding in the reported cases.<sup>1</sup> Thus the surgeon is aided in evaluating the operative indications in a patient with masculinizing changes. If the 17 keto-steroids are high, the pathologic change is probably in the adrenal. If the beta fraction of the 17 keto-steroids is high, the lesion is probably a tumor and not a hyperplasia of the adrenal.

The 11 oxy-cortico steroids with a 17 hydroxyl group were also studied. Talbot and his associates,<sup>1</sup> state that these substances result from adrenal cortical activity and are an index of the rate of secretion of adrenal cortical hormones influencing protein and carbohydrate metabolism. They have found these substances excreted in abnormally large amounts in patients suffering from burns and postoperative conditions as well as in Cushing's syndrome and adrenal cortical virilism. No abnormal elevation was found in simple hirsutism.

## CASE REPORT

A one-year-old white female was referred for admission to the Buffalo Children's Hospital on November 17, 1946, by Dr. Max Landsberger. The mother stated that she had first noted a single black pubic hair when the child was 3 months old. At the age of

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11 months, the Pediatrician first noted an enlarged clitoris and numerous pubic hairs during a routine physical examination. His examination a month previously had not disclosed this abnormality. The child had no complaints and behaved normally.

Examination revealed a healthy appearing young female weighing 25 pounds. Development appeared normal with the exception of the prominent pubic hair and axillary hair. The clitoris was enlarged to four times normal size, also the labia majora. No abdominal masses were found nor were any palpated by rectum. The blood pressure was 100 systolic and 70 diastolic.



FIG 1.—Preoperative appearance of clitoris showing growth of pubic hair

Roentgen-ray studies of the sella turcica and the bones of the skull revealed no abnormalities. The bone age of the long bones were consistent with the child's age. A plain film of the abdomen showed a deformity in the gas-filled duodenum. The duodenum had a concavity in its right border and was displaced to the left as far as the midline. This finding, suggestive of a mass in the region of the right kidney, deforming the duodenum was confirmed after filling the duodenum with barium. It was also illustrated by intravenous pyelography which showed the pelvis of the right kidney to be displaced downward.

Examination of the blood and urine was within normal limits. The serum chlorides were 105 M Eq., non protein nitrogen 22 mg. per cent, sodium 138 M.Eq., cholesterol 175 to 213 mg. per cent, blood sugar 71-123 mg. per cent.

The total 17 keto-steroids were 88.8 mg. in a 24 hour urine sample. The beta fraction of these amounted to 79 mg. The 11 oxy-cortico steroids were 1.07 mg. in 24 hours.

The child's abdomen was explored through an upper transverse incision. A large retroperitoneal tumor mass the size of a man's fist was found at the upper pole of the right kidney. This was excised in toto. The postoperative course was entirely uneventful.

The microscopic description of the tumor by Dr. Kornel Terplan stated that it showed a uniform picture of a mature tubular and alveolar adrenal cortical adenoma of the typical pattern described as the basis of the adreno-genital syndrome. The tumor was well encapsulated and showed some calcification in the hyaline capsule. The tumor cells were rich in glycogen and lipid. There were but few atypical giant nuclei. Two weeks



FIG. 2.—Plain roentgenogram of the abdomen. Arrows show air-filled duodenum deformed by the tumor.

after operation none of the 17 keto-steroids was found in the urine. The 11 oxy-cortico steroids had fallen to .04 mg. in a 24-hour urine sample. A year after operation the total 17 keto-steroid excretion in 24 hours was .2 mg. fraction and the 11 oxy-cortico steroids were .04 mg. (Fractionation of the total 17 keto-steroids was not done because the total value was too low.) At this time the clitoris had diminished in size and the pubic hair was less dense and of finer texture. The child was otherwise normal.

#### COMMENT

Gross<sup>2</sup> in 1940 described numerous neoplasms which produced endocrine disturbances in childhood. These vary greatly. There may be slow growing

tumors of neurogenic origin of the floor of the third ventricle which produce precocious appearance of the secondary sex characteristics. The secondary sex characteristics, however, are always the same as would be expected according to the child's sex. Likewise, a precocious puberty due to a neoplasm is found where the tumor is in the pineal gland. This is always seen in boys. Granulosa cell tumors of the ovary with their masculinizing changes were found producing precocious puberty in girls. No arrhenoblastomas of the ovary with their masculinizing changes were found as they do not occur in children. The youngest recorded patient with arrhenoblastoma was 15. In this review, carcinoma of the adrenal cortex was described as producing

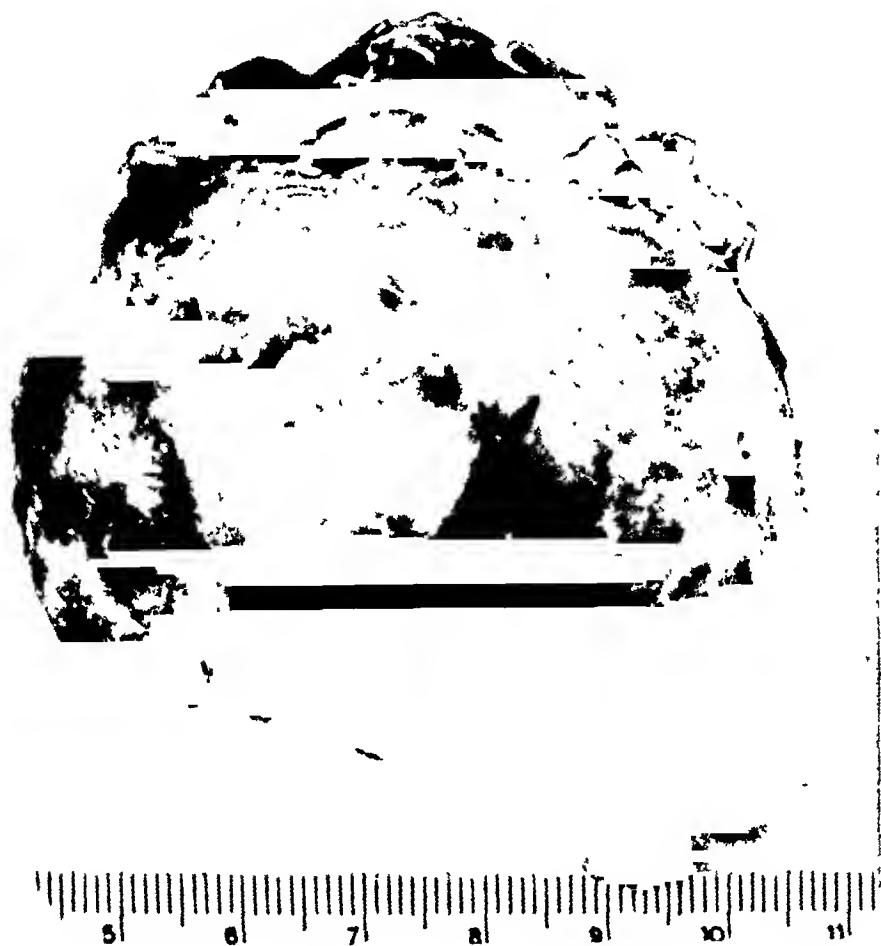


FIG. 3 A.—Gross appearance of the resected adrenal cortical adenoma.

Cushing's syndrome, a masculinizing syndrome in females and a feminizing syndrome in males. A testicular tumor composed of interstitial cells was found to produce early changes in the secondary sex characteristics in a male child.

Talbot, Butler and MacLachlan<sup>2</sup> in 1940 found the 3 beta hydroxy-17-keto-steroids to amount to 10 per cent of the total 17 keto-steroids in normal persons. In two girls with adrenal tumors the proportion was 50 per cent and 63 per cent.



Talbot, Butler and Berman<sup>4</sup> in 1942 stated that patients with adrenal cortical hyperplasia and those with adrenal carcinoma both excrete abnormally large amounts of the 17 keto-steroids. The minimum values of the carcinoma patients approximately coincide with the maximum of the hyperplasia group. Only the group with carcinoma excrete definitely increased quantities of beta 17 keto-steroids.

Callow and Crooke<sup>5</sup> in 1944 summarized the data on 19 reported cases of adrenal cortical tumors. In all but two of these 19 cases the daily output of 17 keto-steroids exceeded four times the average normal excretion. They emphasize that patients with pre-pubertal virilism without adrenal tumors may show relatively the same values (34 to 64 mg. per 24 hours) for urinary

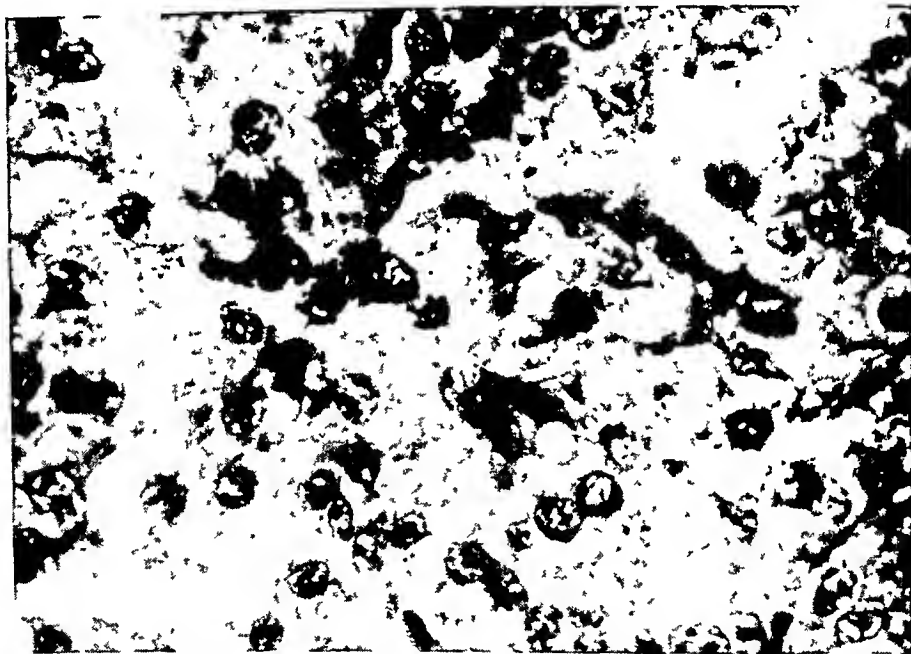


FIG 3 B—Microscopic appearance of the resected adrenal cortical adenoma

17 keto-steroids as the lower range of 17 keto-steroid output in similar patients with adrenal tumors. They report a case of a girl, age 14, whose menstrual periods began at the age of 10. At the age of 12, she developed a large clitoris and hair grew on her face. The total 17 keto-steroids were 90 mg. The beta fraction only accounted for 12 per cent of this total. At operation, normal adrenals and ovaries were found.

Cantarow and Trumper<sup>6</sup> in 1945 stated that the total 17 keto-steroids showed high values in adrenal cortical carcinoma, adrenal cortical hyperplasia and interstitial cell tumors of the testis. They found the beta fraction high in adrenal cortical carcinoma exhibiting the adreno-genital syndrome, also in adrenal cortical carcinoma producing Cushing's syndrome and in one male patient with feminization resulting from adrenal cortical carcinoma.

Broster and Gardener-Hill<sup>7</sup> in 1946 produced a marked improvement in a case of Addison's disease by transplanting an adrenal gland from a case of virilism in a young woman. The donor girl, whose 17 keto-steroids were 29.5 mg. prior to operation, provided an hypertrophied left adrenal gland. Following operation her 17 keto-steroids fell to 5 mg. and she made a satisfactory psychosomatic adjustment. The recipient, who could not be maintained in health without salt and cortical hormone substitution therapy, was able to lead a normal life after having this adrenal gland embedded in her left rectus muscle and anastomosed to the deep epigastric artery.

Dockerty<sup>8</sup> in 1947 described the arrhenoblastoma as the most common functioning ovarian tumor that produces masculinizing changes. While it produces androgenic substances, they are not excreted as 17 keto-steroids. Thus there is a method of differentiating the ovarian masculinizing syndrome from the adrenal masculinizing syndrome. Of much more rare occurrence is the masculinovoblastoma (adrenal-like ovarian tumor). To masculinization, this tumor adds other features of Cushing's syndrome such as hypertension, plethoric obesity, diabetes and polycythemia. The results of hormonal studies in this tumor have been somewhat at variance.

Johnson and Nesbit<sup>9</sup> in 1947 have presented an excellent survey of the literature and details of the 17 keto-steroid excretions in adrenal cortical carcinoma. They found only 32 cases of adrenal cortical carcinoma in which the total 17 keto-steroids had been done and a very few where the beta fraction had been determined. They added three cases of their own in which not only did they find a marked elevation of the total 17 keto-steroids but also the expected increase in the beta fraction which comprised respectively 57, 74 and 80 per cent of the total.

We are deeply indebted to Dr. Fuller Albright of Boston, Massachusetts, in whose laboratory the determination of the keto-steroids were made.

#### CONCLUSIONS

1. This case of pseudo-hermaphroditism with a surgically removed adrenal cortical adenoma has shown the expected elevation of the total 17 keto-steroids (88.8 mg.) and the percentage (87 per cent) of 3 beta hydroxy-17 keto-steroids.

2. The 11 oxy-cortico steroids were found to be four times the average normal in this case. This is likewise consonant with reported studies on adrenal cortical tumors.

3. Follow up studies a year later showed a return of the keto-steroids and oxy-cortico steroids to normal and some regression in the masculinizing changes.

This is presumptive evidence that there has been no recurrence of the tumor.

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# EVALUATION OF THE OPEN JUMP FLAP FOR LOWER EXTREMITY SOFT TISSUE REPAIR\*†

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A RAPID EFFICIENT METHOD of transferring large flaps of skin and subcutaneous tissue to resurface scar defects of the lower extremity has been developed by Cannon, Brown, Lischer, *et al.*, during the recent war. The commonly used abdominal tube pedicles have taken many months to complete and some have been lost in transit. The open jump flap from the abdomen, however, has been found to be much safer, and transfer of large flaps can be completed in a much shorter time.

As the above authors have pointed out, the fundamental principles of the open jump is maintenance of a short broad pedicle throughout all stages of transfer. This assures the flap of an adequate blood supply at all times and allows the use of very large areas of abdominal skin and subcutaneous tissue. A wider area of scar on the leg can be covered with the open jump flap since the abdominal tube is necessarily restricted in its width. The open jump flap method has been used to cover defects from the inguinal region to the sole of the foot, and to the level of a stiff knee. The contralateral arm is often used for a carrier in covering defects of the foot. The open jump flap has the advantage over the cross thigh or cross leg flap in that there is no danger of impairment of circulation in the opposite leg.

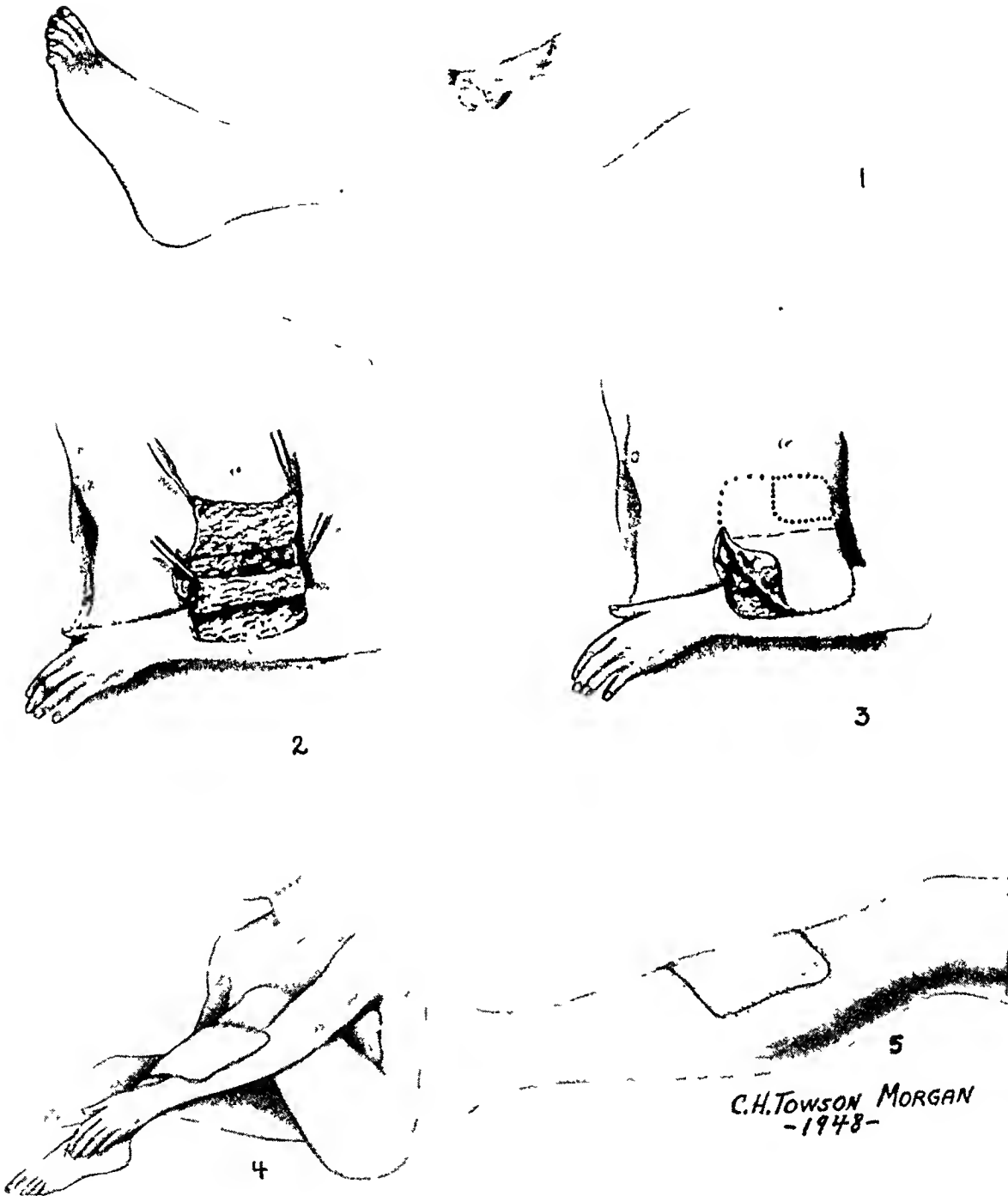
**TECHNIC.** The most important step in preparing an abdominal flap is careful planning. Either arm may be used as a carrier, and the flap may be attached to the radial or ulnar side of the forearm, depending upon which, in the individual case, will allow the most comfortable position during transfer. The flap should always be made one-third larger than the defect to be covered to allow for shrinkage.

A rectangular abdominal flap is raised and dissected back along the deep fascia to preserve the blood vessels running just above the fascia. This flap is so placed on the abdomen that the forearm can be comfortably attached with a minimum of tension. Another rectangular flap of the same width is raised on the forearm. This flap should be one to one and a half inches in length so that when it is turned back an open area of two to three inches in length and the same width as the abdominal flap will be present for attachment

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† This work has been done in association with Colonel James B. Brown, Lieutenant Colonels Bradford Cannon, David Fisher, and Majors Carl E. Lischer, William B. Davis, Stephen Chasko, Andrew M. Moore, Joseph E. Murray, Pierson Checket, and Stephen R. Lewis, and Captains Milton Edgerton, James E. Jensen, Allyn McDowell and Franklin T. Buchanan.



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-1948-

FIG 1.—1. The defect to be covered

2. The abdominal and arm flaps raised and ready for attachment

3. The open jump flap partially sutured to the arm flap. Outer dotted lines indicate remainder of the proposed flap on the abdomen. Inner dotted lines on the left outline area to be undermined at the first delay

4. The open jump flap attached to the leg

5. Completed open jump flap

of the abdominal flap. The two flaps are then sutured together and the open area on the abdomen covered with a skin graft.

After two or three weeks, one-half of the proposed flap remaining on the abdomen is outlined, completely undermined, and resutured in its original position. Ten days later this procedure is repeated on the other half of the proposed flap. The purpose of these delays is to improve the collateral circulation nourishing the flap from the forearm.

Seven to 14 days later the entire flap is raised from the abdomen, and the abdominal defect covered with a split graft. The operating table is now jack-knifed and the patient brought to a sitting position so that the arm and leg may



FIG. 2.—A and B. Stages in construction of an open jump flap for resurfacing scar tissue of the left thigh in a patient who needed a bone graft to the left femur.

be approximated. Skin and scar tissue are excised from the leg defect and the jump flap carefully sutured in place. A pressure dressing is applied and the arm is taped to the leg. The patient's body is held in a flexed position at the hips by a body and leg cast or by long strips of adhesive, as the case requires. This procedure is usually carried out under low spinal anesthesia supplemented on the abdomen by novocaine infiltration for detaching the flap and applying skin graft. This allows the patient to cooperate and avoids the dangers of a thrashing patient awakening from a general anesthesia.

In three weeks the flap is two-thirds detached from the arm, and resutured. Three to seven days later the flap is completely detached and inserted into the leg defect after removing the remaining scar. The flap on the arm may be resutured at this time and usually leaves little more than a linear scar.

## EVALUATION

An attempt has been made to compare the efficiency, period of time required for completion and safety of the abdominal tube pedicle with that of the open jump flap for covering defects of the lower extremity. The abdominal tube pedicle method of resurfacing leg defects was selected for comparison because it was the most common method used by the Plastic Surgical Service at Valley Forge General Hospital and many other plastic surgical services for covering defects too large to be adequately covered by cross leg flaps or by local

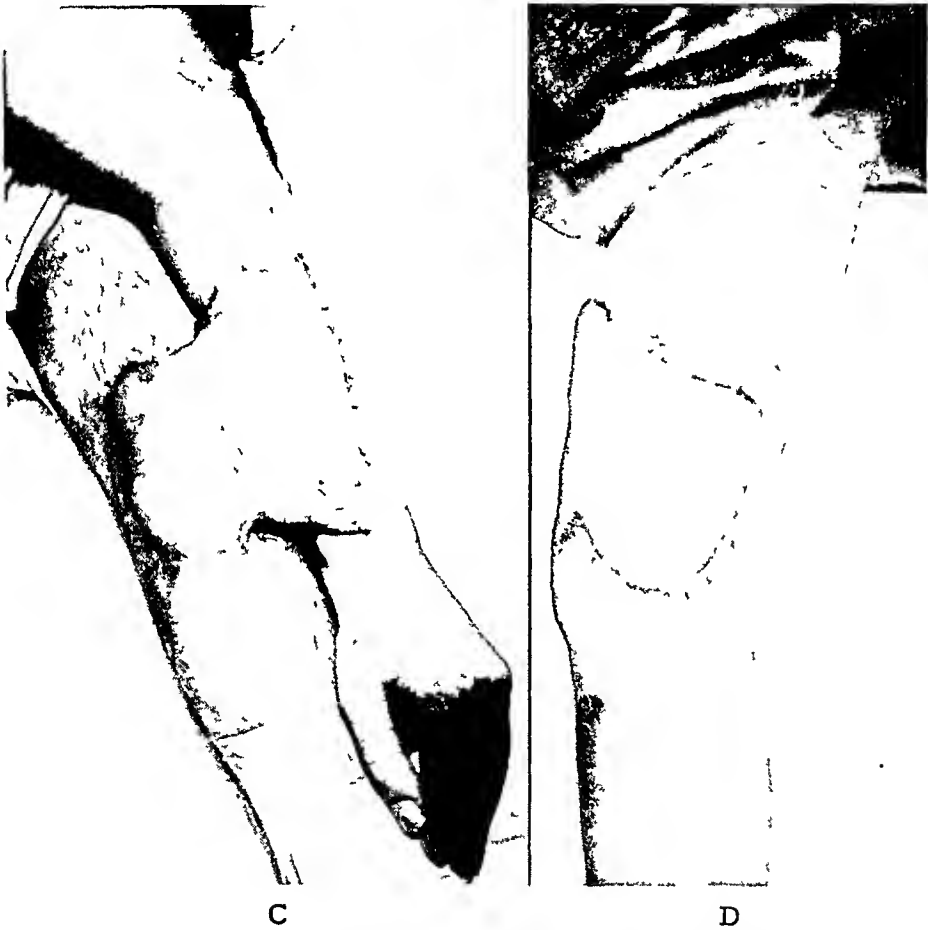


FIG 2—C and D. Stages in construction of an open jump flap for resurfacing scar tissue of the left thigh in a patient who needed a bone graft to the left femur.

flaps. To do this, 26 open jump flaps and 33 abdominal tube pedicles used for lower extremity repair at Valley Forge General Hospital during 1946 and 1947 have been carefully studied and compared. The same surgeons worked on both types of tissue transfer, and the majority of the surgeons performing these procedures has had approximately the same amount of surgical experience.

Of the 33 abdominal tube pedicles studied, seven were unsuccessful to the extent that another abdominal tube or some other method of coverage was

necessary for resurfacing the defect. These tube pedicles were lost at various stages of transfer, usually because of thrombosis in the tube, or necrosis at the distal end. Twenty-six abdominal tube pedicles were successfully completed. It was found that the average length of time that elapsed from the first operation for construction of these 26 abdominal tubes to the date of insertion of the tube into the scar tissue defect was 333 days or approximately 11 months. An average of ten operations was necessary in the 26 completed tubes.

Twenty-six open jump flaps were completed during 1946 and 1947. A corner of one flap was lost, necessitating a small local flap; all other flaps were completely successful. An average of 104 days, or approximately three and one-half months, elapsed between the original operation of attachment of the jump flap to the forearm, and insertion of the flap into the defect. An average of six operations were required in these 26 cases.

The primary objection that has been raised to the open jump flap is the fact that the open under-surface of the flap violates the closed wound principle of surgery. This objection can easily be overcome by covering the under-surface of the flap with a thick split graft. Several of the flaps in the above series were constructed, maintaining a closed wound through all stages; yet these flaps seemed to have no advantages over those left open.

#### SUMMARY

The open jump flap method of repair of soft tissue defects of the lower extremity is described.

Twenty-six open jump flaps and 33 abdominal tube pedicles were reviewed.

Open jump flaps were completed in an average of 104 days and six operations as compared to an average of 333 days and ten operations for completion of the abdominal tube pedicles. Thus, the open jump flaps took only one-third the time required for abdominal tube pedicles.

One open jump flap was partially lost as compared with seven unsuccessful abdominal tube pedicles.

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# CARCINOMA DEVELOPING IN SEBACEOUS CYSTS\*

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WE HAVE RECENTLY REVIEWED THE CASES OF CARCINOMA developing in sebaceous cysts from the material of the Department of Surgical Pathology at the Barnes Hospital. The relatively large amount of material available as well as certain other desirable data appeared to justify a report of our analysis. It has been the practice at this hospital to examine histologically all excised tissue whether apparently benign or not. Sebaceous cysts removed on both the ward service and the private service are routinely submitted for microscopic study, so it is thought that the incidence of malignant transformation may be stated with some accuracy in this report. In three relatively large series reported previously on this subject only Bishop<sup>1</sup> examined microscopically all cysts removed, both Caylor<sup>2</sup> and Stone and Abbey<sup>3</sup> studying microscopically only those cysts in which there was some reason for suspecting a carcinomatous change.

That cutaneous epithelial cysts have several possible origins is well recognized and yet "sebaceous cyst" has come to be applied rather loosely to most cysts of the skin without regard for their origin. This is not without some justification as differentiation may be extremely difficult or impossible particularly when inflammation and degeneration occur. Sebaceous cyst becomes a most infrequent lesion when rigidly defined, as by Warvi and Gates,<sup>4</sup> as retention cysts of sebaceous glands in which secreting sebaceous gland cells must form an integral part of the lining wall. They found only three out of 566 cutaneous epithelial cysts which satisfied these criteria and felt that many more epithelial cysts arise from congenital inclusions or from epithelial cells misplaced by injury. Franke<sup>5</sup> has reported a malignant transformation in what probably was a true traumatic epithelial cyst of the base of the thumb, and one of Collins<sup>6</sup> three cases may represent carcinoma originating in a traumatic epithelial cyst on the palmar aspect of the finger. In none of our cases was there any reason to suspect such a course. Broders and Wilson<sup>7</sup> feel that most so-called sebaceous cysts are better classified as keratomas, and they note several points of differentiation. However, in past reports of carcinoma developing in epithelial cysts, there have been only infrequent efforts made to define the origin of the cyst, and it has been customary to refer to them as "sebaceous cysts." Love and Montgomery<sup>8</sup> reported two carcinomas developing in epithelial cysts other than sebaceous

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cysts and two carcinomas developing in sebaceous cysts, and yet they note that a sharp distinction between the various types of benign cyst has not always been made in their 271 cases. In our material it has not been customary to break down the cysts of the skin of this type into finer subdivisions, and in those cases where carcinoma appears, this differentiation is difficult if not impossible.

It is not always possible to determine from histologic examination alone whether a particular skin cancer has its origin in a cyst. We have in all cases reviewed the history in association with the gross and microscopic

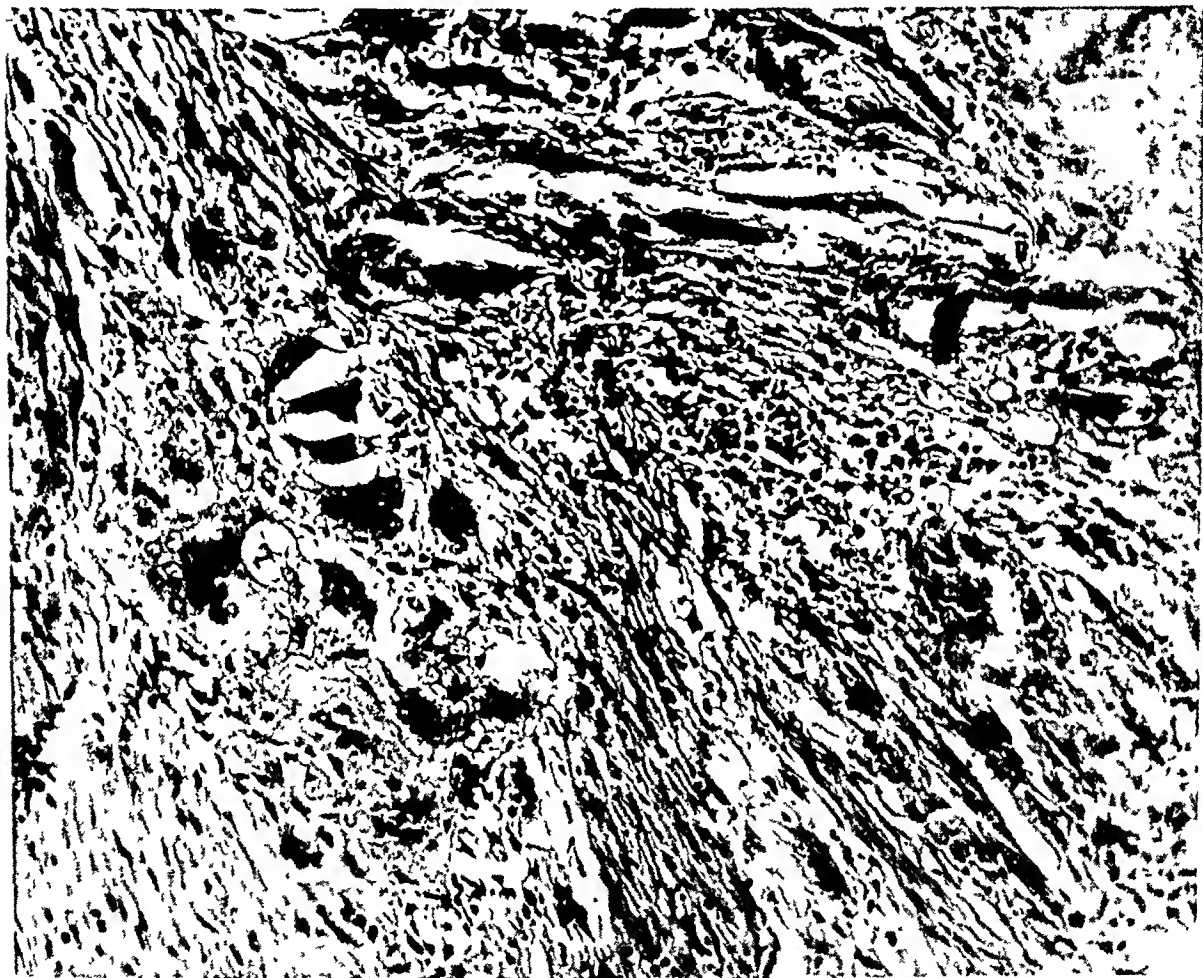


FIG. 1.—Foreign body inflammatory reaction adjacent to sebaceous cyst in which cancer developed. (230x)

findings and in some instances have relied chiefly on the history in determining the origin of a particular lesion. In some cases inflammatory changes in response to the irritable contents of a sebaceous cyst may be seen and give a clue to the cyst origin of the carcinoma (Fig. 1). Even with all available information there may still be some doubt, in which case we may have been inclined to favor the side of cyst origin. In our 14 cases the histologic evidence in nine has been conclusive of the sebaceous cyst origin of the carcinoma; in the five remaining cases we have relied on other evidence in addition to the histologic appearance usually suggestive of cyst origin.

## INCIDENCE

Carcinoma developing in sebaceous cysts has been frequently reported in the literature although usually in small numbers in individual series. However, Ricker and Schwalbe<sup>9</sup> in 1914 collected 43 cases from the literature and there have been a number of cases reported since then.<sup>1-3, 6, 8, 10-15</sup> Bishop<sup>1</sup> reported 11 cases and in his material the incidence of malignant change in a sebaceous cyst was 9.2 per cent, the highest figure in the literature. In other relatively large series Caylor<sup>2</sup> has found the incidence of this change to be 3.4 per cent, Stone and Abbey<sup>3</sup> 2.2 per cent and Love and Montgomery<sup>8</sup> 1.5 per cent. We have identified 14 carcinomas having origin in sebaceous cysts while examining 818 benign sebaceous cysts, an incidence of 1.7 per cent. At the same time 536 squamous cell carcinomas of the skin have been studied, so that our cases make up 2.6 per cent of this group. On the basis of this information, we agree with Love and Montgomery<sup>8</sup> that sebaceous cyst need not be considered as a precancerous lesion. The frequency of malignant change in the group of dermatoses classified as precancerous by Montgomery,<sup>16</sup> namely Bowen's disease, senile keratosis, keratoses resulting from arsenic, tar or radiation and leukoplakia of the mucous membranes, is 20 per cent or more. On the other hand, Sutton<sup>17</sup> and Hellwig<sup>18</sup> criticize the use of the term precancerous at any time.

## AGE, SEX, RACE

The average age of our patients was 51.6 years in accord with previous series<sup>1-3, 6, 9</sup> and only one patient was under 40 years of age. Bishop<sup>1</sup> has noted an average age of 38.2 years of patients with benign sebaceous cysts removed, so the possibility of carcinomatous change appears to be greater with increasing age. The sex distribution was equally divided; there were six males and eight females in our group. One carcinoma occurred in a colored female.

## SITE, DURATION

Seven cases occurred on the scalp, two on the face and one each on the ear, shoulder, arm, forearm, and thigh. In other reports<sup>1-3, 6, 9</sup> the lesions have occurred predominantly above the shoulders with the face and the scalp the most common sites. Approximately one-fourth of all benign sebaceous cysts removed occur on the scalp.<sup>2</sup> No basal cell carcinomas of the scalp originating in sebaceous cysts have been reported in the literature.

Only three of our cases are of known duration greater than two years, one 25 years and two 15 years, while only three cases are of known duration less than 18 months. The relatively long duration of these lesions is apparent.

## TRAUMA, ULCERATION, PREVIOUS EXCISION

The influence of trauma or irritation in the malignant change of sebaceous cysts has been variably considered of importance<sup>8, 13</sup> and of no significance.<sup>1-3</sup> In spite of the frequent appearance of these lesions on the scalp, only one

TABLE I.

Cases	Age	Sex	Site	Dura- tion	Irritation; Trauma	Ulcera- tion	Previous Excision	Recent Change in Character	Preoperative Diagnosis	Histologic Dx	Metas- tases	Follow-up
1. M.T.	43	F	W Scalp	15 yrs.	0	0	0	Gradual increase in size 1 yr.	Seb. cyst	Squamous cell ca.	0	Well, 7 yrs.
2. R.G.	66	M	W Cheek	6 wks.	Pin prick 1 yr. prev.	0	0	0	Epithelioma	Squamous cell ca.	0	Well, 2½ yrs.
3. J.M.	44	M	W Arm	1½ yrs.	Squeezed	0	0	Recent pain	Seb. cyst	Ca. unclassified	Yes	Well, 11½ yrs.
4. F.N.	63	F	C Scalp	15 yrs.	Traumatized with comb	Yes	Yes; 5 yrs. prev.	0	Sarcoma	Squamous cell ca.	0	Well, 7 yrs.
5. J.J.	43	M	W Face	8 wks.	0	0	"Lanced" 5 wks. prev.	Recent increase in size	Tumor	Squamous cell ca.	0	Well, 6 yrs.
6. M.R.	64	F	W Forearm	3-4 wks.	0	0	0	Rapid growth	? Tumor	Squamous cell ca.	0	Died 5 yrs. later of "stroke" with no evi- dence of recurrence
7. H.C.	25	M	W Thigh	?	0	0	0	0	Seb. cyst	Squamous cell ca.	0	No follow-up
8. I.M.	48	F	W Scalp	25 yrs.	0	0	0	Recent increase in size	Seb. cyst	Squamous cell ca.	0	Recurrence—2 yrs. Re-excision else- where, well 4 yrs.
9. C.W.	63	F	W Shoulder	2 yrs.	0	0	Yes; 3 wks. prev.	Recent pain	Infected seb. cyst	Squamous cell ca.	0	Well, 10 yrs.
10. A.K.	75	F	W Scalp	2 yrs.	0	0	0	0	Seb. cyst	Squamous cell ca.	0	Well, 5 yrs.
11. B.W.	53	F	W Scalp	?	0	0	0	0	? Tumor	Squamous cell ca.	0	Well, 3 yrs.
12. A.V.	57	M	W Scalp	Years	0	0	0	Recent increase in size	Calcified seb. cyst	Squamous cell ca.	0	Well, 3 months
13. T.T.	79	M	W Ear	1½ yrs.	0	0	Yes, 6 wks. prev.	0	Basal or squamous cell ca.	Squamous cell ca.	Yes	Unresectable metas- tases
14. R.C.	N	F	X Scalp				No history		Seb. cyst	Squamous cell ca.	0	No follow-up

of our cases reported irritation of the lesion on combing the hair, and only two others of the entire group reported trauma of any other sort. Probably more of these cysts were subject to the trauma of squeezing than is reported, and yet one can find little justification for assuming that trauma is of significance in the carcinomatous change. Only one of our cases gave a history of discharge or ulceration although ulceration in a sebaceous cyst should probably be regarded with suspicion.<sup>2, 3, 8</sup> Three cases had a previous excision within six weeks of treatment at our hospital and one five years previously. This does not appear to be a significant factor in the appearance of cancer in these cases.

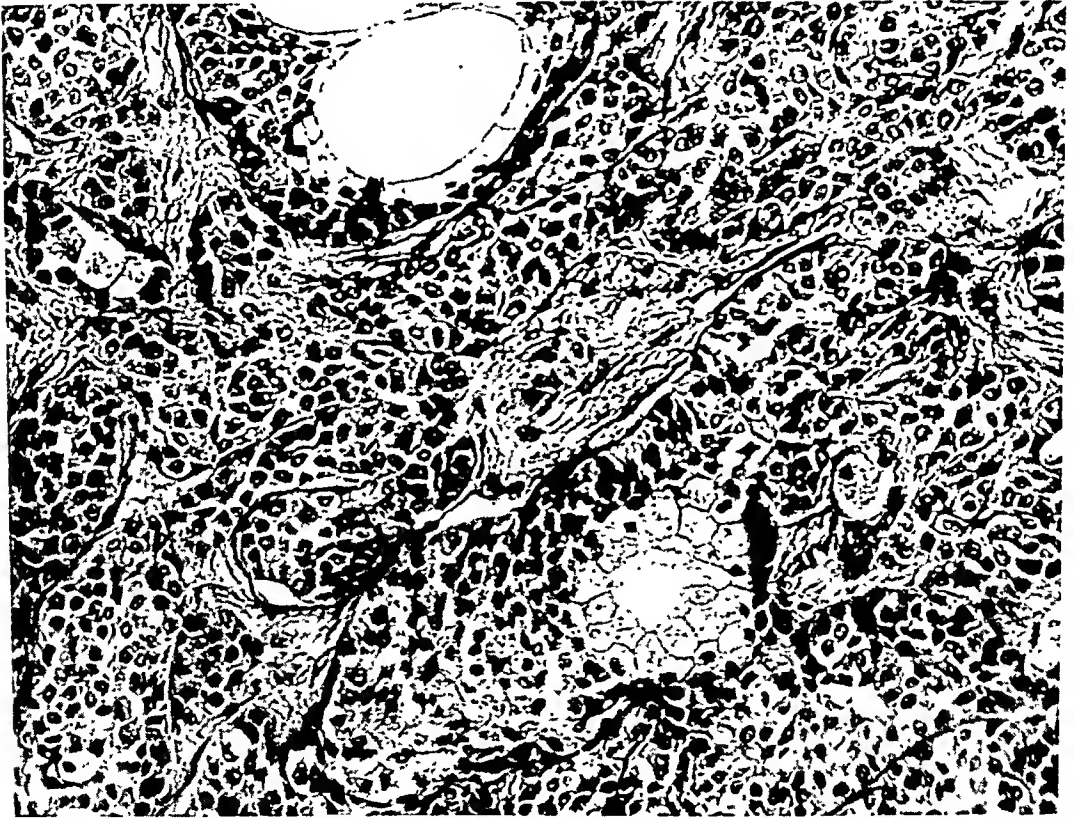


FIG. 2.—Case 1. Compact masses of large clear cells showing gland formation in some areas. (230x)

#### CHANGE IN CHARACTER

In five cases there was observed by the patient a recent change in the character of the lesion. In two instances pain developed and in three cases a recent increase in size of the lesion was noted. Although other reports have not stressed this factor, certainly an increase in size of the lesion should arouse suspicion, particularly if it occurs without evidence of irritation or inflammatory changes.

PREOPERATIVE DIAGNOSIS

As one might suspect, the preoperative diagnosis was incorrect in the majority of cases, and the most common diagnosis was benign sebaceous cyst. In only one instance was the correct diagnosis of squamous cell carcinoma made although the clinician did not definitely associate the lesion with a pre-existing sebaceous cyst. In four other cases tumor of some sort was diagnosed. While this is hardly an enviable record, the errors in diagnosis have not appeared to be of great significance in the final result in these cases.

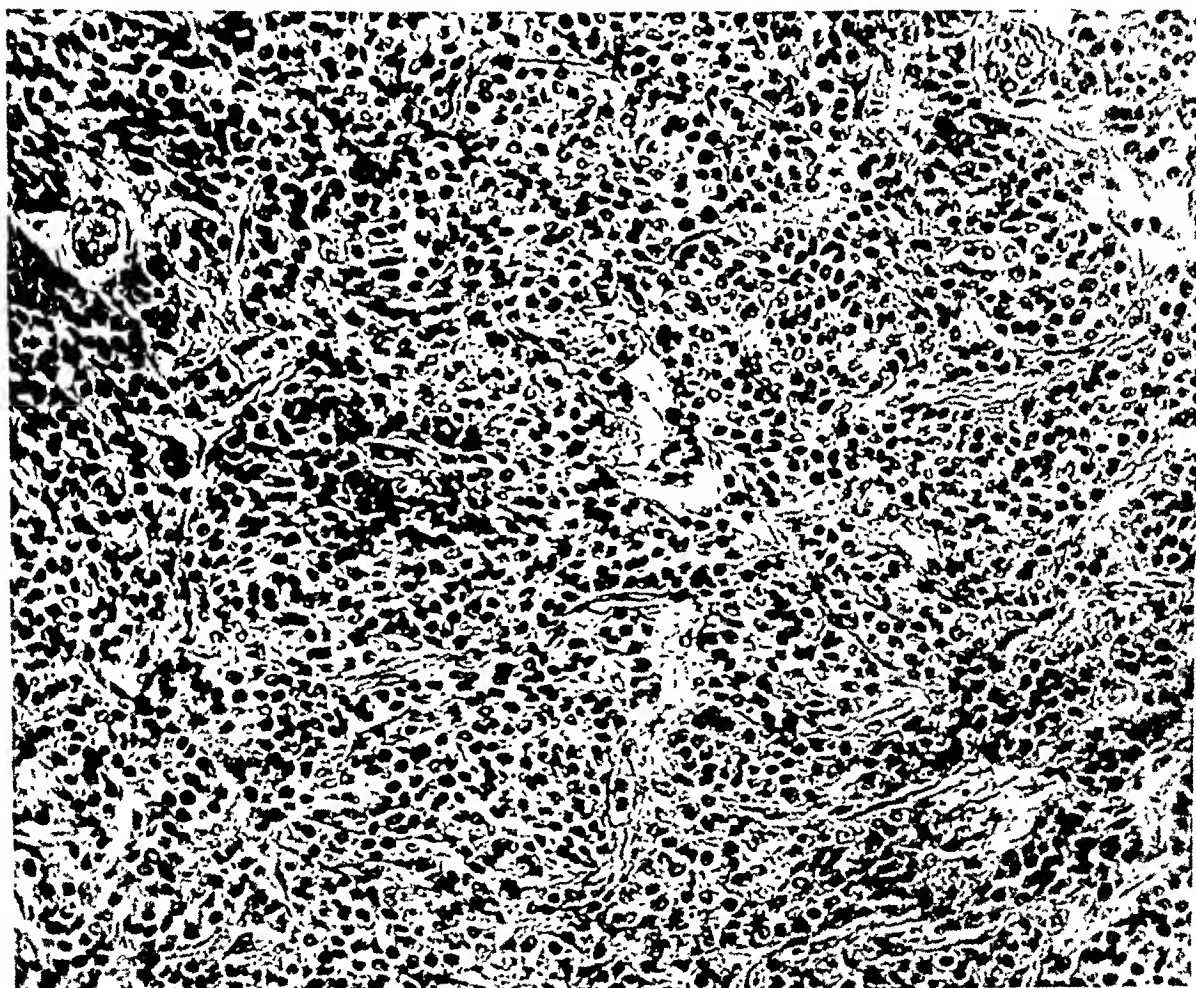


FIG. 3.—Case 1. Metastasis to axillary lymph node showing cells similar in appearance to those of the primary tumor. (170x)

PATHOLOGY

Carcinoma developing in a sebaceous cyst is predominantly of a squamous cell type, although basal cell growth may be found in approximately 15 per cent of cases.<sup>6</sup> However, no basal cell carcinoma of such origin has been reported on the scalp although 35 per cent of malignant sebaceous cysts have been found in this area. Most of the squamous cell carcinomas are well differentiated and of low grade malignancy with marked keratinization and pearl formation (Fig. 5). Havens<sup>19</sup> briefly records a case in which a



melano-epithelioma appeared in a keratoma of the scalp, but this is the only recorded instance in the literature of a growth other than squamous cell or basal cell carcinoma developing in a sebaceous cyst. We have found no specific mention of a carcinoma originating in a sebaceous cyst in which the cells have retained the characteristics of the cells of the sebaceous gland. Of our cases 13 were squamous cell carcinomas showing good differentiation and there were no basal cell growths. One case we have not classified because of its atypical appearance. This case is briefly reported here.

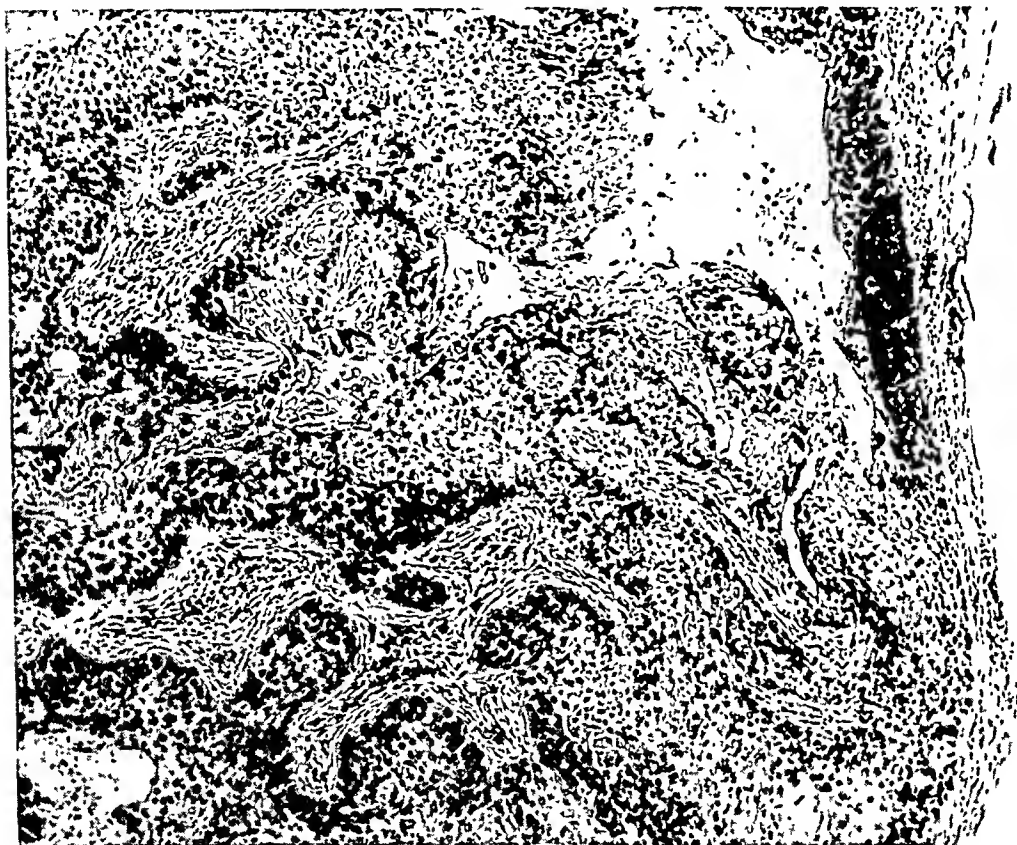


FIG. 4.—Carcinoma in wall of sebaceous cyst with growth into lumen. (85x)

**Case Report No. 1.**—A 44-year-old white male first noted a small pimple on the lateral side of the left arm at its mid-portion 18 months before first seen at Barnes Hospital. This lesion produced a small amount of blood when squeezed. There was a gradual increase in size and finally some pain. On examination the lesion was the size of a hickory nut, movable, attached to the skin and not ulcerated. There were no palpable lymph nodes. The preoperative diagnosis was sebaceous cyst, but on removal a carcinoma was found, apparently originating in a sebaceous cyst and made up of cells with a vacuolated cytoplasm and large vesicular nuclei reminiscent of sebaceous gland cells. The cells were arranged in cords and compact masses with some attempt at gland formation; other areas showed a tendency to squamous cell carcinoma (Fig. 2).

Ten months later several small but palpable, enlarged nodes were found in the left axilla and one enlarged node in the right axilla. There was an apparent increase in size

of the left axillary nodes over a two week observation period, so a radical dissection of the left axilla and a biopsy of the right axillary node was done. Microscopic examination showed the right axillary node to be free of disease but one node from the left axilla was almost entirely replaced by carcinoma made up of compact masses of cells similar in appearance to those of the primary tumor (Fig. 3). The patient has been followed 11½ years with no further difficulty.

The further growth of a carcinoma developing in the wall of a sebaceous cyst may be predominantly inward or outward into the adjacent tissues, and we have seen examples of both types of growth (Figs. 4 and 5). Puhr<sup>10</sup> found inward growth to be more common in cases collected from the literature and Stone and Abbey<sup>3</sup> note that the direction of growth, along with

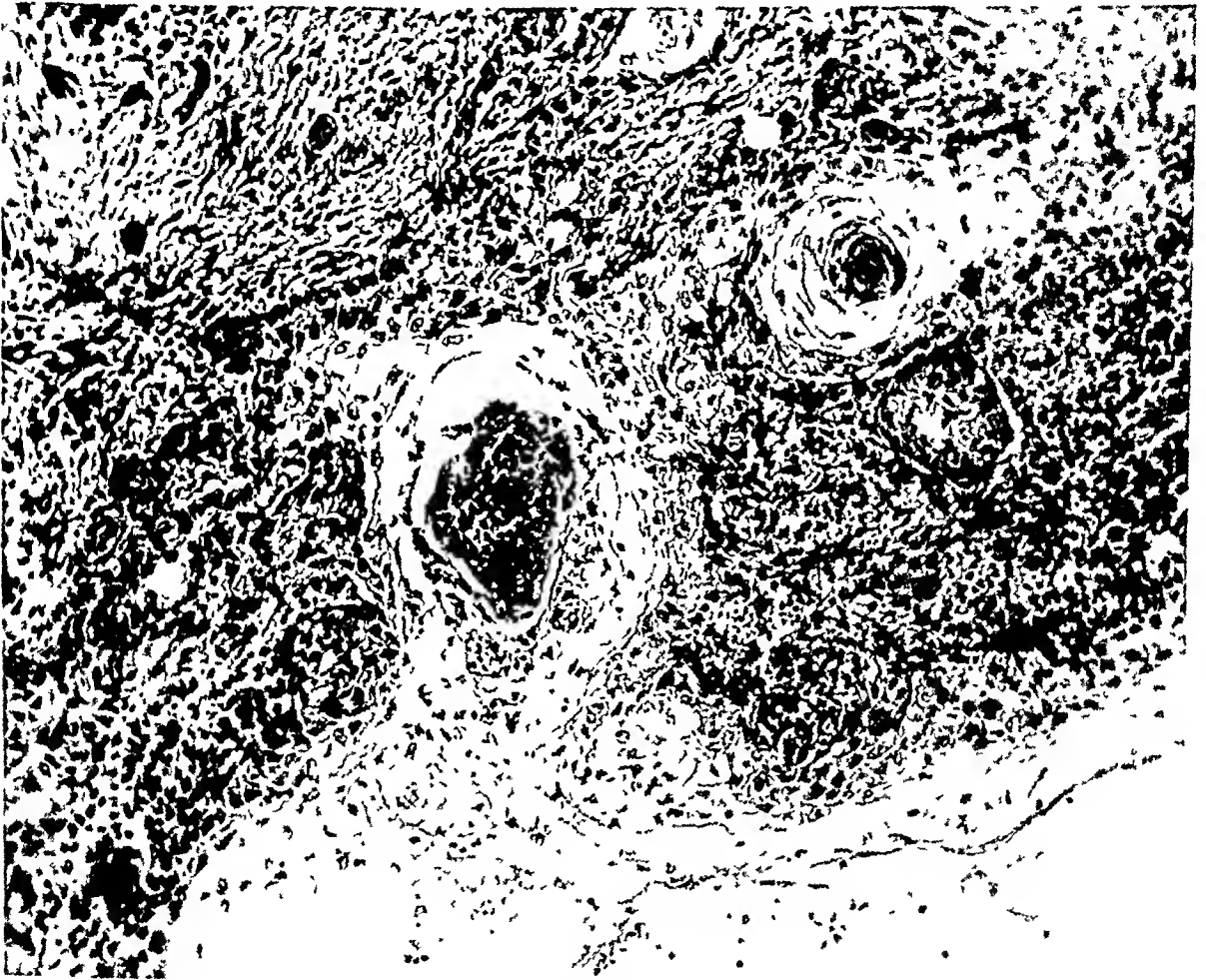


FIG. 5.—Case 2. Well-differentiated squamous cell carcinoma of wall of sebaceous cyst extending into stromal tissue and showing keratinization and pearl formation. (170x)

the differentiation of the tumor, may be of importance in the metastatic behavior of the carcinoma. Actually even regional lymph node metastases have been rare in the case reports of this type of cancer. Caylor,<sup>2</sup> Seff and Berkowitz<sup>13</sup> and Gregersen<sup>15</sup> report one case each with generalized metastases, the case of Gregersen metastasizing to the brain. Two of our cases showed regional node metastases, one described above the second briefly described here.



**Case 2.**—A 79-year-old white male entered Barnes Hospital complaining of a recurrent lesion of the right ear removed by cautery six weeks previously. The lesion of the ear was of 18 months duration. Many other face lesions of unknown character had been previously removed elsewhere. On examination the patient displayed a typical sailor's skin in addition to a crusted, ulcerated lesion of the right ear. The preoperative diagnosis was carcinoma, basal cell or squamous cell type. Histologic examination of the specimen showed a well-differentiated squamous cell carcinoma originating in the wall of a sebaceous cyst (Fig. 5).

Seven months later the patient returned with an ulcerated, indurated mass below the right ear about 5 centimeters in diameter and fixed to the deeper structures. This lesion could be only incompletely removed due to fixation to the transverse processes of the cervical vertebrae. Microscopic examination of this specimen showed a squamous cell carcinoma deep in the subcutaneous tissue. Lymphatic permeation was a prominent feature of the sections, particularly around nerves and one lymph node showed invasion by cancer (Fig. 6a and 6b).

Within the tissue adjacent to any sebaceous cyst one may, upon occasion, find evidence of a foreign body type of reaction, and this has been already mentioned as of some differential value in determining the origin of a carcinoma suspected of arising in a sebaceous cyst. This reaction to the fatty products of the cyst is made up of large mononuclear cells, some with a foamy cytoplasm due to phagocytized fat, collections of small round cells of the lymphocytic type, foreign body giant cells, and a marked fibrosis with cholesterol clefts (Fig. 1).

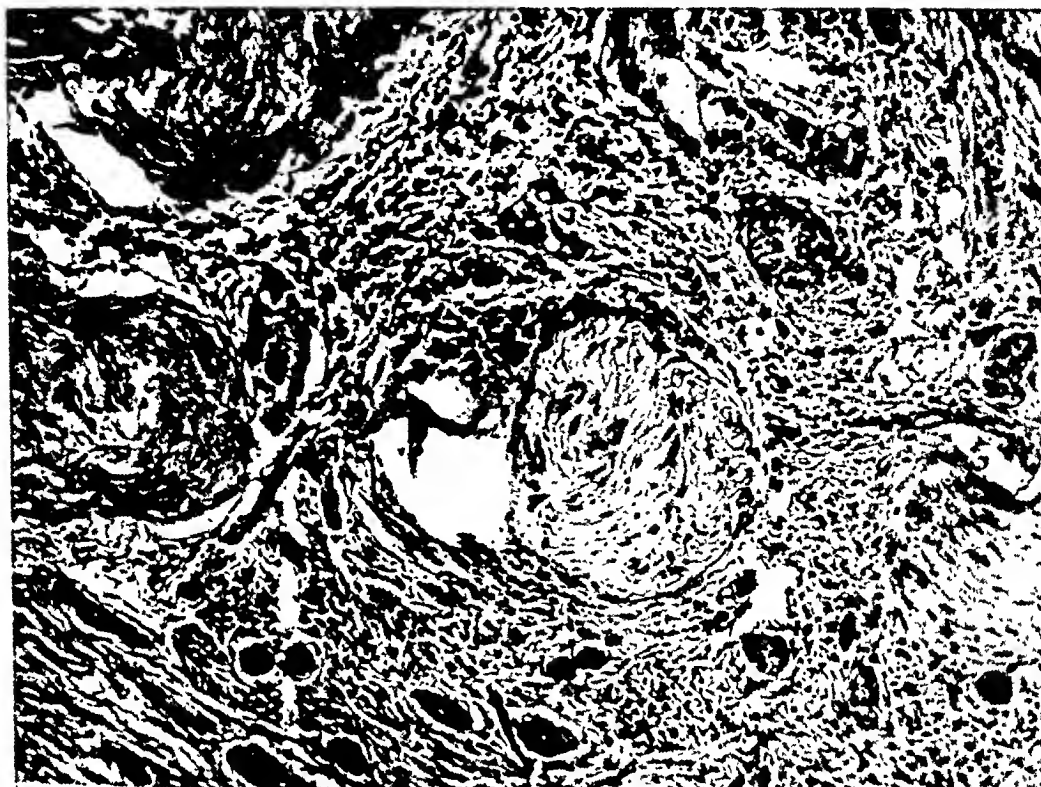
#### TREATMENT

It is not recommended that all sebaceous cysts be excised solely because of the possibility of malignant change, as this alteration is thought to be too rare to justify this treatment. Esthetic reasons constitute a more important indication for removal, and the development of a foreign body inflammatory reaction may lead to significant scarring and prevent easy excision. However, in an individual in the older age group who has an apparent sebaceous cyst of long standing, particularly on the face or scalp, with perhaps ulceration and particularly with some change in character such as an increase in size, a relatively wide excision is indicated because of the possibility of carcinomatous change. A prophylactic regional node dissection is in general not indicated as metastases are rare, but treatment should be individualized and in an extensive lesion of marked anaplasia immediate removal of the regional nodes may be considered. Evidence of regional node metastases subsequent to simple local excision should be treated by block excision of the lymph nodes.

#### PROGNOSIS

The prognosis in this tumor is good although recurrence may be expected if excision is not adequate, and adequate excision depends on a high degree of suspicion in presumed sebaceous cysts which demonstrate some of the characteristics emphasized above. It has been mentioned in the litera-

A



B

FIG. 6A.—Case 2. Perineural lymphatic permeation by metastatic squamous cell carcinoma. (145x).

B.—Case 2. Involvement of peripheral sinus of lymph node by metastatic squamous cell carcinoma. (145x).

ture<sup>2, 3</sup> that recurrence following excision of a sebaceous cyst should arouse one's suspicion regarding its possible malignant nature and indicate a further wide excision. With this we agree, but we believe that it is more important to emphasize the necessity for routine microscopic examination of all sebaceous cysts removed, a proposition that may well be followed for all tissues removed. If this is done, there will be no doubt concerning the proper treatment of recurrent lesions.

Bishop<sup>1</sup> knew of no deaths in his 11 cases; Collins<sup>6</sup> found two deaths in five cases of Grade III or IV and none in 14 cases of Grade I or II in material collected from individual series in which grading had been done. Caylor<sup>2</sup> had one known death with generalized metastases in 12 cases, and Seff and Berkowitz<sup>13</sup> and Gregersen<sup>15</sup> each had one death with generalized metastases. Our own follow-up reveals only one uncured patient who had unresectable lymph node metastases; nine patients are living and well, two and one-half to eleven and one-half years, and one patient died of unrelated cause and without recurrence five years after operation. Thus, ten of eleven patients with sufficient follow-up have been cured.

#### CONCLUSIONS

1. Fourteen cases of carcinoma were found in 832 sebaceous cysts removed, an incidence of 1.7 per cent. This incidence does not justify considering sebaceous cyst as a precancerous lesion.

2. However, in older patients who have had a sebaceous cyst of relatively long duration on the face or scalp, perhaps ulcerated, and in which a recent change in character such as an increase in size has been observed, carcinoma should be suspected.

3. The most common type of cancer found in sebaceous cysts is a well-differentiated squamous cell carcinoma of low grade malignancy, and these usually have not metastasized when first seen. Basal cell carcinomas occur much less frequently.

4. Sebaceous cysts which are suspected of fostering carcinoma should be treated by wide local excision; immediate lymph node dissection is not in general necessary although markedly anaplastic growths may justify such a procedure. Evidence of lymph node metastasis subsequent to previous local excision should be treated by block removal of the nodes.

5. With adequate treatment the prognosis is good. However, if routine histologic examination of all sebaceous cysts removed is not done, adequate treatment of a carcinoma may be delayed and a chance for cure may be lost.

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# COMPARISON OF THE EFFICACY OF THERAPEUTIC AGENTS IN THE TREATMENT OF EXPERIMENTALLY INDUCED DIFFUSE PERITONITIS OF INTESTINAL ORIGIN\*

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AN OPERATION DESIGNED TO PRODUCE a fulminating rapidly fatal peritonitis of intestinal origin was performed on 111 dogs. It was necessary to exclude 18 animals from the group because of complications that interfered with the experiments such as death from anesthesia, air embolism during intravenous therapy, internal fecal fistula, appendiceal avulsion, and hemorrhage. The remaining 93 animals were considered satisfactory for the purpose of evaluating therapeutic agents for the treatment of experimental peritonitis of appendiceal origin.

## METHOD

A method that had previously been developed in this laboratory was used. Laparotomy was performed under sodium pentobarbital anesthesia; the blood supply to the appendix was divided and ligated; feces was expressed into the appendix, filling its lumen completely; the base of the appendix was ligated with flat cotton tape  $\frac{1}{4}$  inch in width; the appendix was crushed by clamping it repeatedly with a large Kocher type hemostat; the spleen and omentum were removed; the animal was given 60 cc. of castor oil by gavage. A small soft rubber tube was placed in the peritoneal cavity and brought out through the laparotomy incision. With the use of aseptic precautions peritoneal fluid for bacterial cultures was aspirated through this tube which was then removed. (Preliminary sampling experiments had revealed definite gross evidence of peritonitis and positive bacterial cultures to be uniformly present six hours after operation.)

The tube also served in some experiments as the means for introducing intraperitoneal therapy. In such experiments, the tube was left in place until the intraperitoneal therapy was discontinued. At the time the tube was removed the skin and subcutaneous tissues were sutured to prevent leakage of peritoneal fluid through the wound. In most of the animals the tubes functioned satisfactorily, but occasionally an animal would withdraw the tube before the experiment was completed.

Simultaneous determinations of blood and peritoneal fluid levels of chemotherapeutic agents were made in some experiments in order to determine

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concentrations and blood-peritoneal fluid relationships during the period of treatment of the infection. The dosage and method of administration of the various chemotherapeutic agents used are described separately with each group of experiments. All experimental animals were given parenteral fluids post-operatively to maintain adequate water and electrolyte intake.

Temperature recordings and leucocyte counts were made in the early experiments but were not done later as they usually were found to be elevated above normal, and this fact did not contribute significantly to the experiment. The appearance, illness, toxicity, and the behavior and habitus of the animals were found to be more valuable indications of the progress of the infection.

Autopsies with bacteriologic and pathologic studies were done at once on all animals that died. Laparotomies with bacteriologic and pathologic studies were performed at weekly intervals on all surviving animals.

CONTROLS

Twenty animals served as controls. All became acutely ill, vomited, grew progressively lethargic and toxic, became comatose and died. The average

TABLE I.—*Experimental Peritonitis*

Untreated Control Series (20 animals)	
Organisms Cultured	Number of Animals
<i>Escherichia coli</i> .....	19
<i>Proteus vulgaris</i> .....	2
<i>Bacterioides</i> .....	2
Aerobic sporeforming bacilli.....	1
<i>Clostridia</i> .....	15
Alpha hemolytic streptococcus.....	3
Beta hemolytic streptococcus.....	5
<i>Streptococcus fecalis</i> .....	8
	16
Hemolytic <i>staphylococcus aureus</i> .....	1
Nonhemolytic <i>staphylococcus albus</i> .....	6
Hemolytic <i>staphylococcus albus</i> .....	3
	10

survival period was 39 hours. Autopsies revealed a diffuse acute inflammatory process throughout the peritoneum. The peritoneal cavity contained thin sanguineous exudate estimated at from 100 cc. to 1000 cc. Varying amounts of fibrinous exudate were deposited about the peritoneal cavity. The appendix was covered with yellow-green exudate and there was no evidence of localization or of a "walling off" process about the appendix.

The bacteria cultured from peritoneal fluid in the untreated control animals are listed in Table I. The organisms most often found were *Clostridia*, *Streptococci* and *Escherichia coli*.

GROUP I. INTRAVENOUS SODIUM SULFADIAZINE

Five dogs in which appendiceal peritonitis had been produced were treated with intravenous sodium sulfadiazine. Therapy was started six hours post-

operatively. Each animal received 4.0 Gm. of sodium sulfadiazine twice daily with Sodium R Lactate 1/6 M to maintain an alkaline reaction in the urine. There was no apparent beneficial effect from sodium sulfadiazine therapy. The progress of the infection was identical with that in untreated control animals. All died. The average survival period was 44 hours. Table II indicates the types of organisms cultured before therapy and at autopsy.

TABLE II.—*Experimental Peritonitis*  
Group I. 5 animals.

Organisms Cultured	Incidence	
	Sodium sulfadiazine 4.0 Gm. given twice daily, intravenously	
	6 Hrs. Postop. (3 Dogs)	Necropsy (5 Dogs)
<i>Escherichia coli</i> .....	1	4
<i>Proteus vulgaris</i> .....	0	2
Aerobic sporeforming bacillus .....	1	0
Clostridia .....	2	5
Alpha hemolytic streptococcus .....	0	2
<i>Streptococcus fecalis</i> .....	0	3
Beta hemolytic streptococcus .....	0	1
Gamma streptococcus .....	1	0
Nonhemolytic <i>staphylococcus albus</i> .....	0	2
Hemolytic <i>staphylococcus albus</i> .....	1	0

TABLE III.—*Experimental Peritonitis*  
Group I.

Blood and peritoneal fluid sulfadiazine levels (milligrams per cent) following the administration of 4.0 Gm. of sodium sulfadiazine intravenously		
Hours	Blood	Peritoneal Fluid
0 .....	0	0
2 .....	24.0	24.0
4 .....	23.0	23.0
6 .....	23.0	23.0
8 .....	23.0	23.0

TABLE IV.—*In vitro Sulfadiazine Susceptibility*  
Group I.

Organisms Cultured	Milligrams Per Cent
<i>Escherichia coli</i> .....	8
<i>Proteus vulgaris</i> .....	8
Alpha hemolytic streptococcus—Not susceptible to .....	10
Beta hemolytic streptococcus .....	8
Gamma streptococcus .....	8
<i>Streptococcus fecalis</i> .....	Not susceptible
Clostridia .....	
Hemolytic <i>staphylococcus albus</i> .....	8
Nonhemolytic <i>staphylococcus albus</i> .....	8

The concentrations of sulfadiazine in the blood and peritoneal fluid in this group are shown in Table III.

Table IV indicates the *in vitro* sulfadiazine susceptibility of the individual organisms cultured from these experiments.

# PERITONITIS OF INTESTINAL ORIGIN

## GROUP II. INTRAPERITONEAL SULFANILAMIDE COMBINED WITH INTRAVENOUS SULFADIAZINE

Five dogs in which appendiceal peritonitis had been produced were treated with intravenous sulfadiazine therapy exactly as described in the preceding group of experiments. In addition, 5.0 Gm. of sulfanilamide were given intraperitoneally through the rubber tube six hours postoperatively just prior to removal of the tube.

Table V shows the blood sulfanilamide concentration following the intraperitoneal instillation of 5.0 Gm. of sulfanilamide.

TABLE V.—*Experimental Peritonitis*  
Group II.

Blood sulfanilamide levels following intraperitoneal instillation of 5.0 Gm. of sulfanilamide	
Time	Blood Level (mg. %)
0.....	0
15 minutes.....	6.20
1½ hours.....	14.05
4 hours.....	15.35
6 hours.....	13.29
8 hours.....	15.50
24 hours.....	6.78

Although the survival period was prolonged in this group (average 80 hours) all animals died. The course of illness and the pathological findings were similar to the untreated controls.

The types of organisms cultured are shown in Table VI. Sulfadiazine mixed culture tests showed most of these organisms to be resistant to sulfadiazine in concentrations up to 12,500 mg. per cent, and sulfanilamide mixed culture tests showed all organisms to be resistant to concentrations of sulfanilamide up to 200 mg. per cent.

TABLE VI.—*Experimental Peritonitis*  
Group II. 5 animals.

Sodium sulfadiazine intravenously, 4.0 Gm. twice daily, and sulfanilamide, 5.0 Gm. six hours post-operatively, intraperitoneally

Organisms Cultured	Incidence	
	6 Hrs. Postop. (5 Dogs)	Necropsy (5 Dogs)
<i>Escherichia coli</i> .....	1	4
<i>Clostridia</i> .....	1	3
<i>Streptococcus fecalis</i> .....	4	5
Hemolytic <i>staphylococcus aureus</i> .....	2	1
Hemolytic <i>staphylococcus albus</i> .....	2	3
Hemolytic <i>staphylococcus citreus</i> .....	1	0
Diphtheroids.....	2	0
Aerophilic lactobacilli.....	0	2



At autopsy peritoneal fluid sulfadiazine levels were found to vary from 44.0 to 182.0 mg. per cent.

### GROUP III. INTRAPERITONEAL SULFASUXIDINE

Five dogs in which experimental appendiceal peritonitis had been produced were treated with intraperitoneal instillations of sulfasuxidine (1.0 Gm. per kilogram of body weight) once daily beginning six hours postoperatively. All animals died. The course of illness, period of survival (average 40 hours) and necropsy findings were similar in every respect to the untreated control series.

Table VII shows the bacteriology in this group of experiments.

TABLE VII.—*Experimental Peritonitis*  
Group III. 5 animals.

Organisms Cultured	Sulfasuxidine 1.0 Gm. per kg. per day intraperitoneally		
	Incidence		
	6 Hrs. Postop. (5 dogs)	1 Day Postop. (2 dogs)	Necropsy (5 dogs)
<i>Escherichia coli</i> .....	2	1	5
<i>Proteus vulgaris</i> .....	..	1	..
<i>Clostridia</i> .....	3	1	2
<i>Streptococcus fecalis</i> .....	4	2	3
<i>Staphylococcus aureus</i> .....	2	0	0
<i>Staphylococcus albus</i> .....	2	0	1
Diphtheroids.....	..	..	1

Undissolved sulfasuxidine varying from small to considerable amounts was found spread throughout the peritoneal cavity at autopsy. Occasionally considerable accumulations of the drug were found to be pocketed in fibrin. The concentration of sulfasuxidine in the peritoneal fluid at autopsy was found to be from 6.0 to 42.0 mg. per cent (measured as sulfathiazol). Table VIII shows increasing sulfasuxidine resistance of the bacterial flora and the concentration of the drug in these experiments.

TABLE VIII.—*Sulfasuxidine Susceptibility Tests*  
Group III.

	6 Hours Postoperatively	Necropsy
<i>Escherichia coli</i>	Susceptible 3.12– 6.24 mg.%	Most susceptible at 50.0 mg.%
<i>Proteus vulgaris</i>		Not susceptible at 50.0 mg.%
<i>Clostridia</i>	Susceptible 0.28–50.0 mg.%	Not susceptible at 50.0 mg.%
<i>Streptococcus fecalis</i>	Most unsus- ceptible to 50.0 mg.%	Some not susceptible and some susceptible to 50.0 mg.%
<i>Staphylococcus aureus</i>	Susceptible 0.25–50.0 mg.%	Not susceptible at 50.0 mg.%
Diphtheroids		Not susceptible at 50.0 mg.%

### GROUP IV. STREPTOMYCIN

(INTRAMUSCULARLY BEGINNING SIX HOURS POSTOPERATIVELY)

Ten dogs in which appendiceal peritonitis had been produced were treated with intramuscular injections of streptomycin. Therapy was started six hours postoperatively. Each animal received 2 Gm. of streptomycin daily in divided

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doses of .33 Gm. given intramuscularly at four-hour intervals. Two of the ten animals recovered from the acute peritonitis under streptomycin therapy, but a fecal fistula suddenly developed in one of the animals on the sixth postoperative day and it expired the following day. The remaining eight animals died with the same acute signs of peritonitis as the controls, but their average survival period was 92 hours, as compared to an average survival period of 39 hours for the untreated control animals. The only pathogenic organisms that were consistently susceptible to the streptomycin in vitro were *Escherichia coli* and they usually persisted in their growth in vivo and were found at autopsy. The Streptococci and Clostridia were uniformly resistant to streptomycin both in vitro and in vivo.

TABLE IX.—*Experimental Peritonitis*  
Group IV. 10 animals.

Organisms Cultured	Incidence	
	6 Hrs. Postop. (7 dogs)	Necropsy (9 dogs)
<i>Escherichia coli</i> .....	6	9
<i>Proteus vulgaris</i> .....	0	1
<i>Bacterioides</i> .....	1	0
Aerobic sporeforming bacillus.....	1	1
Clostridia.....	5	8
Alpha hemolytic streptococcus.....	1	1
Beta hemolytic streptococcus.....	2	4
Gamma streptococcus.....	2	1
<i>Streptococcus fecalis</i> .....	1	2
Nonhemolytic <i>staphylococcus albus</i> .....	2	2
Hemolytic <i>staphylococcus albus</i> .....	1	1
Hemolytic <i>staphylococcus aureus</i> .....	1	1

The one streptomycin-treated animal that survived without complications was lost inadvertently during induction of anesthesia prior to exploratory laparotomy on the seventh postoperative day. Gross examination of the peritoneal cavity revealed evidence of subsiding peritonitis. Cultures of the peritoneal exudate taken before the streptomycin therapy was started grew the usual bacterial flora of the colon.

Table IX shows the types of organisms cultured from the animals in this experiment.

Table X gives the streptomycin susceptibility of the bacterial organisms cultured from the peritoneal cavity prior to treatment of this group of animals with streptomycin.

Table XI shows blood and peritoneal fluid streptomycin concentrations following intramuscular administration of streptomycin.

## GROUP V. STREPTOMYCIN

(INTRAMUSCULARY BEGINNING IMMEDIATELY POSTOPERATIVELY)

Five dogs in which appendiceal peritonitis had been produced were treated with streptomycin beginning immediately after operation. Each animal was

given 2 Gm. of streptomycin daily in divided doses of .33 Gm. intramuscularly every four hours. The course of infection in these animals was similar to that in the untreated control animals. All died. However, the average survival period of these animals treated with streptomycin was 75 hours as compared with an average survival period of 39 hours for the untreated control animals.

Table XII indicates the bacteria cultured in this group of experiments.

TABLE X.—*Experimental Peritonitis*  
Group IV.

Streptomycin susceptibility	
Organisms	Units per Cubic Centimeter
<i>Escherichia coli</i> .....	1.78–20.0
<i>Proteus vulgaris</i> .....	7.1 –80.0
Bacterioides .....	Not susceptible
Aerobic sporeforming bacillus .....	3.0
<i>Pseudomonas aeruginosa</i> .....	Not susceptible
Clostridia .....	Not susceptible
Alpha hemolytic streptococcus .....	Not susceptible
Beta hemolytic streptococcus .....	1.3 –28.5
Gamma streptococcus .....	3.57
<i>Streptococcus fecalis</i> .....	Not susceptible
Non hemolytic <i>staphylococcus albus</i> .....	14.6
Hemolytic <i>staphylococcus albus</i> .....	3.0 – 8.0
Hemolytic <i>staphylococcus aureus</i> .....	2.0

TABLE XI.—*Experimental Peritonitis*  
Group IV.

Blood and peritoneal fluid streptomycin concentrations (units per cubic centimeter) following the administration of 0.33 Gm. of streptomycin intramuscularly		
Hours	Blood	Peritoneal Fluid
0 .....	0	0
1 .....	20	0
2 .....	40	20
3 .....	40	20
4 .....	20	10

TABLE XII.—*Experimental Peritonitis*  
Group V. 5 animals.

Streptomycin 2.0 Gm. daily (.33 Gm. intramuscularly every 4 hours) beginning immediately after completion of operation		
Organisms Cultured	Incidence	
	6 Hrs. Postop. (4 dogs)	Necropsy (5 dogs)
<i>Escherichia coli</i> .....	2	3
Bacterioides .....	0	1
Clostridia .....	3	4
Alpha hemolytic streptococcus .....	0	1
Beta hemolytic streptococcus .....	1	0
Gamma streptococcus .....	1	0
<i>Streptococcus fecalis</i> .....	2	3
Nonhemolytic <i>staphylococcus albus</i> .....	2	0
Nonhemolytic <i>staphylococcus aureus</i> .....	1	0
Diphtheroid bacillus .....	2	0

GROUP VI. STREPTOMYCIN INTRAPERITONEALLY

Ten dogs in which peritonitis was produced were treated with intraperitoneal instillation of streptomycin. Therapy was started six hours postoperatively.

A. In the first group of five animals, three were given 0.4 Gm. intraperitoneally on two occasions on the day of operation, and 0.4 Gm. daily thereafter. Two animals were given 0.8 Gm. twice daily on the day of operation, and 0.8 Gm. once daily thereafter. All animals died with acute peritonitis. The course of illness and autopsy findings were the same as those in the untreated control animals. However, the average survival period of the animals treated with intraperitoneal streptomycin was 87 hours compared with an average survival period of 39 hours for the untreated controls.

Table XIII shows the bacteriologic findings six hours postoperatively and at necropsy in this group of experiments. Additional cultures taken at 22, 30, 48 and 72 hours postoperatively were similar to those made at necropsies.

TABLE XIII.—*Experimental Peritonitis*  
Group VI-A 5 animals.

Organisms Cultured	Streptomycin intraperitoneally 0.4 to 1.6 Gm. daily	
	Incidence	
	6 Hrs. Postop. (4 dogs)	Necropsy (5 dogs)
<i>Escherichia coli</i> .....	2	4
<i>Clostridia</i> .....	3	5
Alpha hemolytic streptococcus.....	2	4
Gamma streptococcus.....	0	1
<i>Streptococcus fecalis</i> .....	1	0
Nonhemolytic <i>staphylococcus albus</i> .....	2	1

B. Up to this point in vitro laboratory tests and animal experiments had demonstrated considerable evidence that the pathogenic bacterial flora of experimental peritonitis were resistant to streptomycin in concentrations and doses that ordinarily would be considered safe to use in therapy of human patients. It was decided to attempt to use intraperitoneally doses of streptomycin that would be more likely (based on in vitro streptomycin susceptibility tests) completely to destroy all pathogenic organisms. Four (4.0) Gm. of streptomycin were instilled intraperitoneally in each of five dogs six hours after completion of the operation to produce experimental peritonitis. All dogs died within 10 to 30 minutes after either their first or second instillation of streptomycin. The average survival period was 12 hours. These deaths occurred from respiratory failure due to the toxic effect of streptomycin on the medullary centers. Blood streptomycin concentration was 160 units per cc. 10 minutes after intraperitoneal instillation of 4.0 Gm. of streptomycin.

Bacterial cultures of the peritoneal fluid were taken at necropsy in four of the animals in this group. In three animals the cultures were sterile. *Escherichia coli* and *Clostridia* were cultured from the peritoneal fluid

specimen taken at the necropsy of the fourth animal. All animals had gross evidence of acute diffuse peritonitis at autopsy.

Table XIV indicates the bacteriologic findings in this group of experiments.

TABLE XIV.—*Experimental Peritonitis*  
Group VI-B 5 animals.

Streptomycin intraperitoneally 4.0 Gm. twice daily beginning  
6 hours postoperatively

Organisms Cultured	Incidence	
	6 Hrs. Postop. (4 dogs)	Necropsy (4 dogs)
<i>Escherichia coli</i> .....	3	1
<i>Clostridia</i> .....	3	1
Alpha hemolytic streptococcus .....	2	0
Beta hemolytic streptococcus .....	1	0
Gamma streptococcus .....	1	0
Hemolytic staphylococcus aureus .....	1	0

#### GROUP VII. PENICILLIN

Commercially available penicillin was given intramuscularly in divided doses every four hours to three groups of animals. Penicillin therapy was started six hours following operations for the production of experimental peritonitis of appendiceal origin. Each animal in the first group received 100,000 units of penicillin per day, the second group 200,000 units of penicillin per day, and the third group 500,000 units of penicillin per day. All animals that survived received treatment for six days.

A. One out of three animals in the first group (treated with 100,000 units of penicillin daily for six days) survived and two died with diffuse peritonitis. The course of illness, pathology and bacteriologic cultures in the animals that died were similar to those seen in the untreated control animals. The one animal that survived had gross pathologic evidence of a subsiding peritonitis when examined at exploratory laparotomy on the seventh day. Bacteriologic cultures made on that day grew Gamma streptococci and Clostridia. Apparently the laparotomy reactivated the infection for the animal died five days later with acute diffuse peritonitis (no attempt was made to treat this animal with penicillin following the exploratory laparotomy).

B. In the second group (treated with 200,000 units of penicillin daily for six days) two animals survived and three died with acute diffuse peritonitis. The course of the disease, pathologic and bacteriologic findings in the animals that died were similar to those in the untreated control series. The animals that survived had positive bacterial cultures and gross evidence of subsiding acute peritonitis at exploratory laparotomies performed on the seventh day. One survivor died four days after exploratory laparotomy with fulminating diffuse peritonitis. The other survivor was examined at necropsy one month postoperatively (during this period of one month the animal appeared and

behaved like a normal healthy dog) at which time the peritoneal cavity contained a slightly increased amount of peritoneal fluid and minute scattered granulations over parietal and visceral peritoneum and the cultures grew *Escherichia coli*.

C. All the animals in the third group (treated with 500,000 units of penicillin daily for six days) survived the acute phase of experimentally induced peritonitis. At first they were acutely ill, but soon all evidence of toxicity and illness disappeared. Exploratory laparotomies performed on the seventh postoperative day revealed evidence of subsiding peritonitis, and bacterial cultures grew a mixed bacterial flora. One animal died with fulminating acute diffuse peritonitis due to reactivation of the infection at the exploratory laparotomy on the seventh day. The other four animals were examined again at laparotomy on the 30th day when positive bacterial cultures were obtained in three dogs and all had scattered pin point size granulations throughout the peritoneum. One animal was apparently healthy for two months postoperatively, then acute diffuse peritonitis developed (pure culture of *Escherichia coli*) with extensive exudation and necrosis, and the animal died.

Two months postoperatively exploratory laparotomies on the remaining survivors still revealed minute scattered granulations, but the bacterial cultures were sterile. The results are summarized in the following table:

TABLE XV.—*Experimental Peritonitis*  
Group VII. 13 animals.

Penicillin (commercial) given intramuscularly in divided doses every 4 hours				
Group	Daily Penicillin Dosage (units)	Number of Dogs	Recovered	Died
A.	100,000	3	1	2
B.	200,000	5	2	3
C.	500,000	5	5*	0

\* One dog died with *Escherichia coli* peritonitis two months after treatment.

Table XVI shows the bacteriology in these groups of animals treated with commercial penicillin.

Table XVII shows blood and peritoneal fluid concentrations following the administration of 16,667 units of commercially available penicillin intramuscularly.

GROUP VIII. PENICILLIN AND STREPTOMYCIN THERAPY COMBINED

Five animals in which peritonitis of appendiceal origin was produced were treated with penicillin and streptomycin for six days, beginning six hours postoperatively. Each animal received 500,000 units of penicillin and 2.4 Gm. of streptomycin daily in divided doses, given at four-hour intervals by intramuscular administration. All five animals in this group survived. The findings were almost identical to those in the animals of Group VII-C which were treated with 500,000 units of penicillin daily.

TABLE XVI.—*Experimental Peritonitis*  
Group VII.

Bacteriology—commercial penicillin series				
Group A. 100,000 Units Daily	6 Hours (3 dogs)	7 Days (1 dog)	Necropsy (2 dogs)	
<i>Escherichia coli</i> . . . . .	3	0	2	
<i>Pseudomonas aeruginosa</i> . . . . .	0	0	1	
<i>Bacterioides</i> . . . . .	0	0	1	
<i>Clostridia</i> . . . . .	3	1	2	
<i>Alpha streptococcus</i> . . . . .	3	0	2	
<i>Beta streptococcus</i> . . . . .	1	0	2	
<i>Gamma streptococcus</i> . . . . .	1	1	1	
<i>Streptococcus fecalis</i> . . . . .	0	0	1	
Group B. 200,000 Units Daily	6 Hours (5 dogs)	7 Days (2 dogs)	30 Days (1 dog)	Necropsy (4 dogs)
<i>Escherichia coli</i> . . . . .	2	1	1	2
<i>Clostridia</i> . . . . .	5	2	0	3
<i>Alpha hemolytic streptococcus</i> . . . . .	0	0	0	1
<i>Beta hemolytic streptococcus</i> . . . . .	1	0	0	1
<i>Streptococcus fecalis</i> . . . . .	4	2	0	3
<i>Staphylococcus albus</i> . . . . .	1	0	0	0
<i>Staphylococcus aureus</i> . . . . .	1	0	0	0
Group C. 500,000 Units Daily	6 Hours (5 dogs)	7 Days (5 dogs)	30 Days (4 dogs)	Necropsy (60 days 1 dog)
<i>Escherichia coli</i> . . . . .	1	5	3	1
<i>Aerobacter aerogenes</i> . . . . .	0	3	0	0
<i>Clostridia</i> . . . . .	2	5	2	0
<i>Streptococcus fecalis</i> . . . . .	0	4	1	0
<i>Beta hemolytic streptococcus</i> . . . . .	1	0	0	0
<i>Gamma streptococcus</i> . . . . .	1	0	0	0
<i>Staphylococcus aureus</i> . . . . .	1	0	0	0

TABLE XVII.—*Experimental Peritonitis*  
Group VII.

Blood and peritoneal fluid concentrations of penicillin (units per cubic centimeter) following intramuscular injection of 16,667 units of penicillin

Hours	Blood	Peritoneal Fluid
0 . . . . .	0	0
1 . . . . .	1.20	0.62
2 . . . . .	2.50	1.20
3 . . . . .	0.62	0.31
4 . . . . .	0.15	0.31

TABLE XVIII.—*Experimental Peritonitis*  
Group VIII. 5 animals.

Penicillin (500,000 units daily) and Streptomycin (2.4 Gm. daily) given intramuscularly in divided doses at 4 hour intervals

Organisms Cultured	Incidence		
	6 Hours (4 dogs)	7 Days (5 dogs)	28 Days (1 dog)
<i>Escherichia coli</i> . . . . .	1	3	0
<i>Clostridia</i> . . . . .	3	4	1
<i>Streptococcus fecalis</i> . . . . .	0	3	1
<i>Nonhemolytic staphylococcus albus</i> . . . . .	1	1	1
<i>Diphtheroid bacillus</i> . . . . .	1	0	0

Table XVIII shows organisms cultured in this group of experiments.

Table XIX shows penicillin and streptomycin susceptibility of organisms cultured before therapy, and after seven days of therapy with streptomycin and penicillin.

TABLE XIX.—*Experimental Peritonitis*  
Group VIII.

Bacterial susceptibility tests. Cultures made from animals receiving penicillin and streptomycin therapy (Units per cubic centimeter)				
Organisms Cultured	6 Hours		7 Days	
	Penicillin	Streptomycin	Penicillin	Streptomycin
<i>Escherichia coli</i> .....	25.0	35.0	—200.0	300–600.0
<i>Clostridia</i> .....	0.57	1.05	12.5–100.0	17.25–300.0
<i>Streptococcus fecalis</i> .....	0.028	0.05	13.12– 50.0	9.3 –150.0
<i>Nonhemolytic staphylococcus albus</i> .....	0.57	1.05		

#### GROUP IX. PENICILLIN-X (INTRAMUSCULAR)

Penicillin containing 15 to 25 per cent penicillin-x was given to a group of ten animals in which experimental peritonitis of appendiceal origin had been produced. Treatment was started six hours after the surgical procedure to produce peritonitis. The penicillin-x was given intramuscularly in divided doses at four-hour intervals. A total dosage of 100,000 units a day for six days was given each animal. Nine animals survived and one expired after living 76 hours after the onset of peritonitis. All survivors recovered very rapidly from the initial acute illness on penicillin-x therapy. Recovery from toxicity and lethargy occurred very early, and normal appetite and activity were observed during the first few days of treatment in these animals.

Bacteriologic cultures made from the peritoneal fluid from the animal that died grew *Escherichia coli*, *Proteus vulgaris*, *Bacterioides* and an aerobic spore-forming *Bacillus*, all relatively resistant to penicillin-x. Exploratory laparotomies performed seven days postoperatively on the survivors showed evidence of a subsiding acute peritonitis, and bacterial cultures made at that time grew penicillin-resistant gram negative flora, *Clostridia* (3 animals) and a penicillin resistant *streptococcus fecalis* (1 animal).

Exploratory laparotomies performed 30 days later revealed no evidence of the peritonitis and all bacterial cultures made at this time were sterile.

Table XX indicates the blood and peritoneal fluid concentrations of penicillin following intramuscular administration of penicillin-x.

Table XXI gives the results and bacteriologic findings in this group of experiments.

#### GROUP X. PENICILLIN-X (INTRAPERITONEAL)

Five dogs in which experimental appendiceal peritonitis had been produced were treated with intraperitoneal instillations of penicillin containing 15 to 25 per cent penicillin-x, beginning six hours postoperatively. Each animal received 100,000 units of penicillin (with 15 to 25 per cent penicillin-x) twice



the first day, and 100,000 units daily thereafter for six days. Two animals survived and three died. One died during the course of therapy, one died immediately after the cessation of therapy, and the third animal died several days after the completion of therapy.

TABLE XX.—*Experimental Peritonitis*  
Group IX.

Blood and peritoneal fluid concentrations of penicillin (units per cubic centimeter) following intramuscular injections of 16,667 units of penicillin containing 15 to 25 per cent penicillin-x		
Hours	Blood	Peritoneal Fluid
0.....	0	0
1.....	2.50	1.20
2.....	2.50	0.62
3.....	2.50	0.62
4.....	0.31	0.62

Necropsy in the three fatal cases showed a diffuse peritonitis, and bacteriologic cultures grew the usual mixed flora from the colon. The animals that died were acutely ill and toxic. The two animals that survived were examined by exploratory laparotomy two weeks and four weeks postoperatively. Diffuse, extensive granulations up to ¼ inch in thickness were found throughout the peritoneal cavities of these two animals and bacterial cultures revealed persistence of the pathogenic organisms. These two animals were

TABLE XXI.—*Experimental Peritonitis*  
Group IX. 10 animals.

Penicillin (15 to 25 per cent penicillin-x) intramuscularly, 100,000 units daily (16,667 units every 4 hours) for 6 days			
Organisms Cultured	Incidence		
	6 Hrs. Postop. (8 dogs)	7 Days (9 dogs)	30 Days (5 dogs)
<i>Escherichia coli</i> .....	6	5	0
<i>Proteus vulgaris</i> .....	1	2	0
<i>Aerobacter aerogenes</i> .....	0	1	0
<i>Pseudomonas aeruginosa</i> .....	0	1	0
Aerobic sporeforming bacillus .....	0	1	0
<i>Clostridia</i> .....	8	3	0
Alpha hemolytic streptococcus .....	5	0	0
Beta hemolytic streptococcus .....	2	0	0
<i>Streptococcus fecalis</i> .....	0	1	0
Nonhemolytic <i>staphylococcus albus</i> .....	4	0	0
Hemolytic <i>staphylococcus albus</i> .....	2	0	0
D phtheroid bacillus .....	1	0	0

acutely ill at the onset of the peritonitis, but signs of toxicity rapidly decreased during intraperitoneal penicillin therapy and their appearance and behavior seemed entirely normal at the time of the follow-up exploratory procedures.

Table XXII shows the results and the bacterial cultures in this group of experiments. There was no alteration of penicillin susceptibility in the bacteria during the course of intraperitoneal therapy with penicillin-x.

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Table XXIII shows blood and peritoneal fluid penicillin levels in this group of experiments.

SUMMARY

Table XXIV summarizes the results of these experiments in the treatment of peritonitis of appendiceal origin in dogs with sulfonamides and antibiotics.

TABLE XXII.—*Experimental Peritonitis*  
Group X. 5 animals.

Penicillin (15 to 25 per cent penicillin-x) 100,000 units intraperitoneally daily for 6 days				
Organisms Cultured	Incidence			
	6 Hours Postop. (8 dogs)	Necropsy (3 dogs)	15 Days (2 dogs)	30 Days (2 dogs)
<i>Escherichia coli</i> .....	5	3	2	2
<i>Proteus vulgaris</i> .....	2	1	0	0
Clostridia.....	5	3	2	2
Alpha hemolytic streptococcus.....	3	2	0	2
Beta hemolytic streptococcus.....	2	2	2	1
Gamma streptococcus.....	1	0	0	0
<i>Streptococcus fecalis</i> .....	1	0	1	0
Nonhemolytic <i>staphylococcus albus</i> .....	1	0	2	0
Hemolytic <i>staphylococcus albus</i> .....	2	2	0	0
Hemolytic <i>staphylococcus aureus</i> .....	2	0	0	0
Diphtheroid bacillus.....	1	0	0	0

TABLE XXIII.—*Experimental Peritonitis*  
Group X.

Blood and peritoneal fluid concentrations of penicillin (units per cubic centimeter) following the intraperitoneal instillation of 100,000 units of penicillin (15 to 25 per cent penicillin-x)		
Hours	Blood	Peritoneal Fluid
0.....	0	0
1.....	19.96	80.00
2.....	9.95	80.00
3.....	4.99	9.95
4.....	1.20	4.99
10.....	.....	0

CONCLUSION

Fulminating diffuse peritonitis was produced in 93 dogs by dividing the vascular supply to the appendix; ligating the base, and crushing the appendix. The omentum and spleen were removed. Twenty untreated control animals died with acute diffuse peritonitis from bacterial infection with intestinal organisms. The average survival period was 39 hours.

Sulfonamide therapy with (1) intravenous sodium sulfadiazine (5 dogs), (2) intraperitoneal sulfasuxidine (5 dogs), and (3) combined intraperitoneal sulfanilamide and intravenous sodium sulfadiazine (5 dogs) apparently had no beneficial effect. All died with peritonitis similar to that observed in the control animals. However, the survival period in the sulfanilamide-sulfadiazine group was prolonged to 80 hours.

Streptomycin therapy given intramuscularly (10 dogs) and intraperitoneally (5 dogs) apparently prolonged the survival period of dogs with experimental appendiceal peritonitis to averages of 75 to 92 hours in 14 out of 15 dogs. One animal survived. However, doses of streptomycin that effectively controlled the organisms in the peritoneal cavity caused death from the toxic effect of streptomycin (apparently on the medullary respiratory center).

Commercially available penicillin given intramuscularly at four-hour intervals daily in doses of 100,000 units (3 dogs) 200,000 units (5 dogs) 500,000 units (5 dogs), and 500,000 units combined with streptomycin 2.4 Gm. was definitely beneficial in the treatment of experimental appendiceal peritonitis. All animals receiving 500,000 units of penicillin daily survived.

TABLE XXIV.—*Comparison of Therapeutic Agents for the Treatment of Experimental Peritonitis of Appendiceal Origin.*

*Treatment	Number of Dogs	Recovered	Died	Average Survival Hours
Controls—untreated.....	20	0	20	39
1. Sulfadiazine 4 Gm. twice daily intravenously.....	5	0	5	44
2. Sulfadiazine 4 Gm. twice daily intravenously and Sulfanilamide 5 Gm. intraperitoneally.....	5	0	5	80
3. Sulfasuxidine intraperitoneally.....	5	0	5	40
1.0 Gm. per kilogram of body weight daily				
4. Streptomycin intramuscularly, 2.0 Gm. daily..... (started 6 hours postoperatively)	10	1	9	92
5. Streptomycin intramuscularly, 2.0 Gm. daily..... (started immediately postoperatively)	5	0	5	75
6-A. Streptomycin intraperitoneally.....	5	0	5	87
0.4 to 1.6 Gm. daily				
6-B. Streptomycin intraperitoneally 4.0 Gm. daily....	5	0	5	12
7-A. Penicillin intramuscularly 100,000 units daily.....	3	1	2	37
7-B. Penicillin intramuscularly 200,000 units daily.....	5	2	3	65
7-C. Penicillin intramuscularly 500,000 units daily.....	5	5	0	..
8. Penicillin intramuscularly 500,000 units daily, and Streptomycin intramuscularly 2.4 Gm. daily.....	5	5	0	..
9. Penicillin-x (15 to 25 per cent) intramuscularly ..... 100,000 units daily	10	9	1	76
10. Penicillin-x (15 to 25 per cent) intraperitoneally ..... 100,000 units daily	5	2	3	135

\* All therapy was begun 6 hours postoperatively unless otherwise specifically designated. All intramuscular therapy was given in equally divided doses at four-hour intervals.

Penicillin containing 15 to 25 per cent penicillin-x in doses of 100,000 units daily intramuscularly (10 dogs), and intraperitoneally (5 dogs) was effective in the treatment of experimental appendiceal peritonitis. Nine out of 10 animals treated intramuscularly, and 2 out of 5 animals treated intraperitoneally with penicillin-x recovered.

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# GIANT CELL TUMOR OF THE SACRUM: A CASE REPORT\*†

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## CASE HISTORY

This 29-year-old white male was admitted to the hospital November 7, 1945. In April, 1945, he fell from a truck in England. No pertinent injury was sustained, but one week later there appeared pain in the lower back in the sacral region. One month later he noticed slight swelling in that region. Patient has not noted exaggeration of the pain by motion of the trunk, but states it is accentuated by prolonged sitting. During the past 3 to 4 months he has noted numbness in the posterior aspect of the left leg. There has been approximately 40 pounds weight loss with illness.

Roentgenograms taken on September 15, 1945, revealed a marked osteolytic process involving the distal four sacral segments and the coccyx. It was noted that the neoplasm had broken through the cortices in numerous places and had infiltrated the pre- and post-sacral soft tissues, resulting in a grapefruit-sized mass, most of which was in the pelvis.

Physical examination revealed a well-developed, undernourished, white male in no distress. Findings are limited to lower back and rectum. There is a large ovoid pulsating swelling which is located centrally in the region of the sacrum. Over the mass are many dilated blood vessels. Slight tenderness to palpation is present. Motion of the back does not accentuate the discomfort. Knee jerks are hyperactive bilaterally with absent ankle jerks. Area of hypesthesia involves the posterior aspect of the left thigh. Heart and lungs are normal.

Rectal examination reveals a protrusion of the sacral mass against the rectal wall which displaces the rectum anteriorly. Pulsation can be felt by examining finger. The outline is smooth, edge circumscribed, and no invasive tendencies are noted. Auscultation reveals no bruit. There is no thrill. Blood pressure: 130/80. R.B.C.: 4,350,000. Hemoglobin: 85 per cent. W.B.C.: 7,400. Coagulation time: 3 minutes. Bleeding time: 1½ minutes. Urine: negative.

Roentgen-ray report: The entire sacrum with the exception of its proximal end is destroyed, replaced and expanded in all diameters with a thin shell of subperiosteal new bone remaining irregularly distributed over the surface of the tumor and a few strands of bone remaining with it. The coccyx is partially destroyed.

## DISCUSSION

Differential diagnosis involved consideration of either a pulsating tumor or aneurysm. Aneurysm could be readily eliminated because of the position where its presence would be rare, the fact that there was no thrill, bruit, or murmur, and the presence of the bony lacework in the tumor as viewed by roentgen-ray. The type of pulsation was definitely expansile. The question naturally arose as to whether or not the pulsation was a transmitted one. Rectal examination with bimanual palpation revealed the extent of pulsation

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to be the same, as near as one could tell, in the intrapelvic portion of the mass as in that portion located just beneath the skin. Finally, there was no history of the usual etiologic factors such as significant trauma, syphilis, operation or congenital nature. Perhaps of great importance was the fact that there seemed to be substance in the wall of the pulsating mass at every point accessible to the examining hand or finger.

Our attention was now given to the type of tumor. Tumors in this region are rare. They include chordomas, dermoids, ependymomas, teratomas,<sup>5</sup> Ewing's tumor, giant cell tumor, neuro- and fibro-sarcomata. Of this group of



FIG. 1.—Preoperative X-ray of giant cell tumor.

possibilities, teratomas, dermoids, and neuro-fibromas usually arise from the ventral surface of the sacrum and seldom destroy that bone. Chordomas and ependymomas do not pulsate as a rule, and rarely is pulsation observed in a fibrosarcoma. Therefore, if neoplasm is the cause of the pulsating mass, it appears that the benign giant cell tumor or the malignant Ewing's tumor must be the responsible type. Rectal findings disclosed circumscription and slight mobility of the tumor, characteristics which suggested benignity. Aspiration biopsy was deemed inadvisable due to the pulsating nature of this tumor and possible subsequent intraneoplastic hemorrhage. However, it was accomplished and the tumor proven to be of the benign giant cell type.

The choice of a method for treatment was a serious matter. One fact seems to be clear in the minds of competent bone tumor students. Benign giant cell

tumors<sup>3, 4, 6, 7, 8</sup> can be treated either by radiation or surgery independently, but the combination of radiation therapy and surgery produces poor results. The advocates of both forms of therapy insist that if their method is chosen, it must be adequately and completely employed. Geschickter and Copeland<sup>11</sup> feel that "Surgery is the treatment of choice for giant cell tumors in general, and make no exception for pulsating giant cell tumors." Herendeen<sup>6</sup> is of the opinion that radiation successfully handles giant cell tumor in the majority of cases. Anticipating that this tumor may not be completely removed by surgical extirpation and realizing the attending dangers of surgical removal,



FIG. 2.—Postoperative X-ray of pelvis.

several radiotherapists were consulted in the matter. Each was hesitant, due to the pulsating nature of the neoplasm and fear that too much radiation would be necessary regardless of the division into numerous small doses, which would result in skin necrosis and probably alarming hemorrhage. Some questioned the ability of radiation to completely destroy the tumor and others felt that the resulting fibrosis of the skin and rectal wall would be deleterious, and one was concerned with the possibility of rectal fistulae. With these unenthusiastic remarks in favor of radiation in mind, we considered the surgical attack as the method from which the best result could be achieved. It meant sacrifice of

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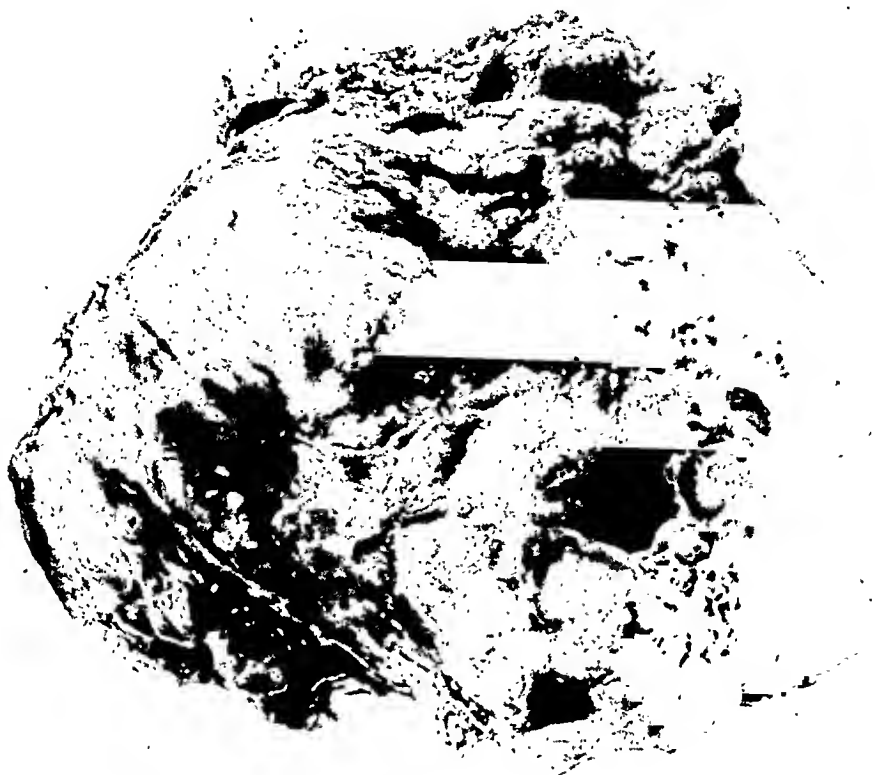


FIG. 4.—Anterior view of giant cell tumor.

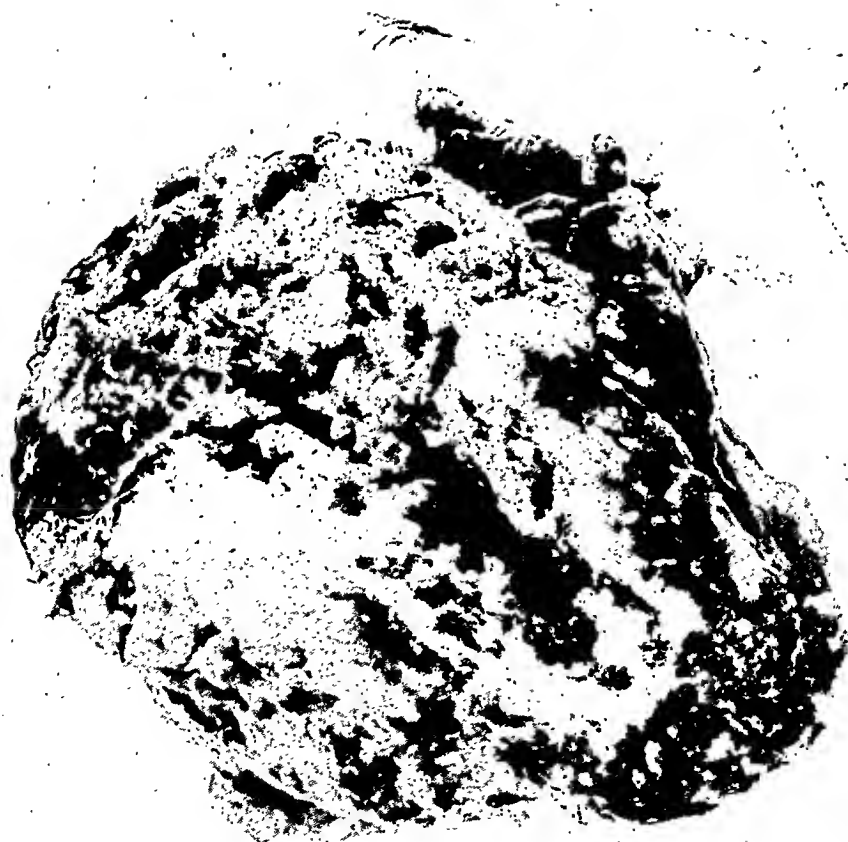


FIG. 3.—Posterior view of giant cell tumor.



sacral segments II, III, IV, V, the coccyx, and all the sacral nerves below  $S_I$  or  $S_{II}$ . We felt this not to be untenable even though it meant partial or complete paralysis of the bladder and rectal sphincters. But the ability of the surgeon to completely control hemorrhage and at the same time completely remove the tumor presented a hazardous problem.

Therefore, consideration for a surgical attack upon the tumor was at hand. The benignity of the tumor led us to postulate that if the tumor could be freed from its posterior attachments and the blood supply controlled, that it would be a relatively simple matter to establish a cleavage line and dissect

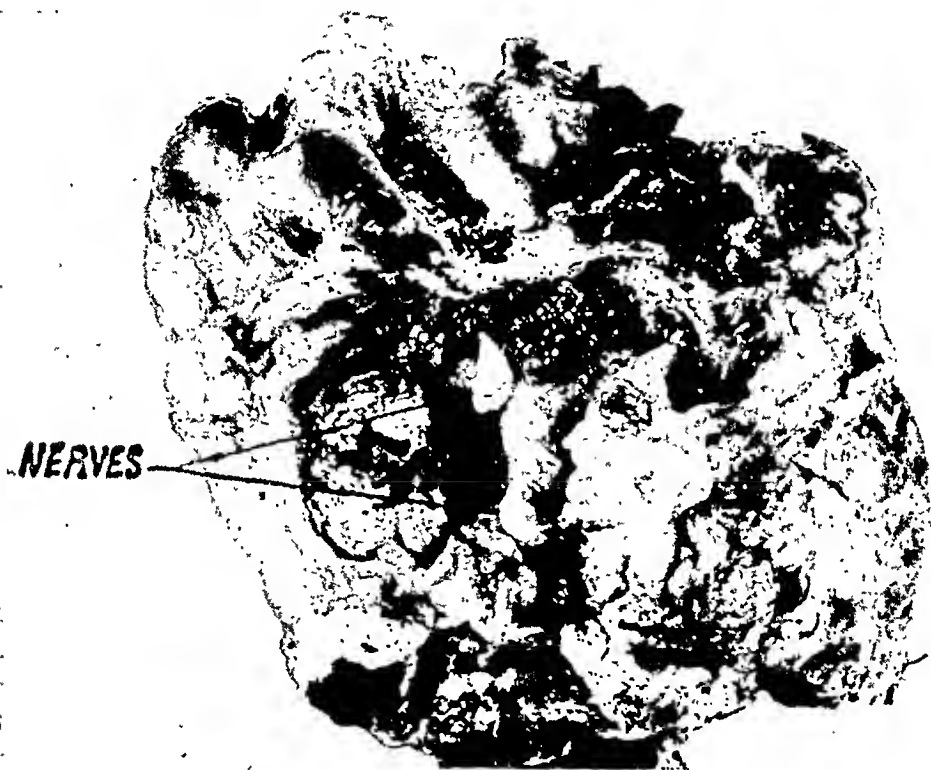


FIG. 5.—Superior surface of giant cell tumor.

it free of the rectum. If the tumor arose from the sacrum, the blood supply could be assumed to be dependent upon the middle or lateral sacral vessels and the hypogastric arteries. Hope for controlling these vessels posteriorly was vain.

*Operations.* On November 20, 1945, the first operation was done with the patient in the prone position. An elliptical incision was made in the skin at the projected lateral and longitudinal margins of the tumor. This was made slowly, because of profusion of subcutaneous blood vessels which were clamped and ligated with fine black silk. The lateral flaps were reflected with the same vascular difficulty. This exposed the fascia of the gluteus maximus muscle, the pre-sacral fascia and the pre-coccygeal fascia. The next excursion entailed the incision of these fasciae, encountering a greater number of blood vessels than in the subcutaneous tissue. When this was completed, the pulsating tumor arose from its bed and the pulsations were more pronounced. At the coccygeal end of

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the mass, we were able to define a cleavage line for attempted dissection from the rectum, but the vascularity was so great that after 5 hours of total operating time, the procedure was abandoned and the skin closed with interrupted silk sutures. Two 500 cc. blood transfusions were given while the patient was in the operating room.

The patient recovered rapidly from this major attempt at posterior removal.

The location of the tumor was again considered in relation to its main blood supply which, we now correctly conjectured, must be in the hypogastric artery or one of its branches. Therefore, it was deemed wise to explore the tumor by laparotomy to determine the source and possibility of controlling the blood supply.

On December 4, 1945, a left rectus incision was made near the midline. When the peritoneal cavity was opened and small intestines displaced into the upper abdomen, the large tumor could be seen to be residing in the space behind the sigmoid, which

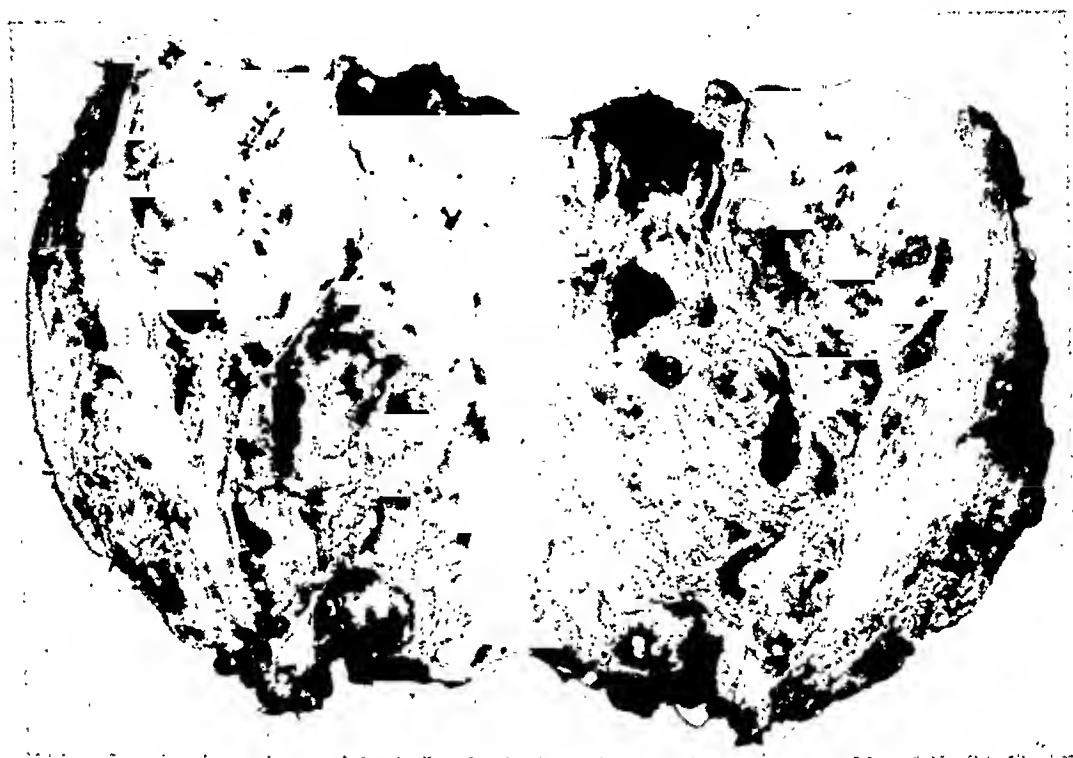


FIG. 6.—The sectioned giant cell tumor.

pushed this bowel anteriorly to the level of the anterior peritoneum. The common iliac vessels were exposed and when occluded, cessation of the pulsations in the tumor was observed. The hypogastric vessels were huge and could be seen entering the growth about one inch distal to their exit from the common iliac artery. Occlusion of these vessels also completely stopped the pulsation. The hypogastric vessels were now doubly ligated and transected. Although the pulsations had ceased, our experience posteriorly in the first operation had commanded great respect for the vascularity of this tumor, and to prevent any chance of collateral supply from the arteries below the hypogastric, both common iliac arteries were occluded with umbilical tapes. The laparotomy wound was closed with through and through silver wire sutures and the patient was placed in the prone position. The old posterior wound was now reopened and the cleavage plane at the coccygeal end reestablished. With great ease and little bleeding, we were able to incise the gluteus maximus muscle and then by dissecting under the tumor, freed the tumor from the rectum, sigmoid, and a few lateral muscular attachments. Now the tumor was attached only to the inferior border of the first sacral vertebra. By chiselling across the substance of good bone, the removal was completed. The tumor was torn in one area during the chiselling process. The bone was finally debrided of its neoplastic invasion by rongeur. Very little bleeding accompanied this removal.

The rectal wall was not injured. The skin was closed loosely with drainage of the huge dead space. During the dissection an attempt was made to save as many of the sacral nerves as possible. The first sacral nerves were intact, but the remainder were necessarily sacrificed.

The patient was again placed in position for laparotomy, the wires removed, exposure regained, and the tapes removed from both common iliac vessels. The tapes had been left in place for 2 hours and 45 minutes. The abdominal wall was closed in layers with



FIG. 7.—Healed posterior wound.

silk, and the patient returned to the ward in good condition. Dorsalis pedis and posterior tibial arteries were pulsating after the tapes were removed, and have functioned properly ever since.

Microscopic section showed this to be an extremely vascular but typical benign giant cell tumor with areas of bony tissue scattered throughout its substance.

*Course.* A retention catheter was placed immediately following the operation. An examination of the rectal sphincter revealed a total lack of sphincter tone. From the interruption of the pre-sacral nerve and lower sacral nerves, urinary and rectal incontinence were expected. The patient experienced a smooth postoperative course. The laparotomy wound healed per primam, but the sacral wound separated, the dead space granulated to the skin level, and this area was finally healed by Thiersch grafting in

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April, 1946. The patient was ambulatory on the 12th postoperative day and remained ambulatory except for a short time following the grafting operation. Paralysis of the urinary sphincter persisted and is handled by the regimen instituted by the use of a Cunningham clamp. The rectal sphincter, although paralyzed, has not been the cause of great discomfort. A daily bowel movement in the early morning was the established habit, and soiling takes place only when infrequent diarrhea appears.

The patient's general condition began to improve and during the course of four months, he had regained weight to the normal amount, became strong, and appeared in the best of health. He went home on furlough for long periods of time. About 9 months after the operation, he was rehospitlized with a minimal chest lesion, thought to be tuberculous. It was considered as a matter of safety to regard the infection as tuberculous, in spite of negative sputa and gastric washings. He was treated for this chest lesion for a period of 6 months. At this time the pulmonary lesion had completely disappeared. His weight was normal and the status of the urinary and rectal sphincters was unchanged. The presence of the tumor, with its attending malnutrition, and the rigors of the operation may have been factors contributing to the onset of the tuberculous infection.

*Follow-Up.* The patient has been able to walk without great difficulty although he complains of weakness in the legs and numbness along the back of the thighs and legs. Upon discharge in the fall of 1946, the rectal and urinary sphincters were not functioning, there was anesthesia over a small area perianally and hypesthesia extending down the posterior aspects of both legs and in the heels. In response to a questionnaire, the patient sent a reply indicating the following status on March 4, 1948, approximately 2 years and 3 months following the radical removal of the tumor. He performs light work around a small shop and his house, and claims that the legs "play out" after vigorous exercise. There is no control of urinary or rectal sphincters. Cunningham clamp is worn, constipating diet is followed. These handicaps are not as distressing as the leg weakness, according to the patient. His weight is normal, appetite good. Roentgenograms of the chest and sacral region were done in December, 1947, which reveal maintenance of the disappearance of the pulmonary lesion and non-recurrence of the tumor. It appears reasonable to expect permanent cure of this benign tumor, now that there is no clinical or roentgenological evidence of recurrence after the passage of 2 years and 3 months postoperatively.

### SUMMARY

1. Resection of the coccyx and sacral vertebrae II, III, IV and V has been accomplished in a patient with a large pulsating benign giant cell tumor originating in the sacrum.
2. The method employed is described. It entailed laparotomy, ligation of the hypogastric arteries and temporary occlusion of the common iliac arteries before successful posterior resection could be done.

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# CHOLEDOCHUS CYST ASSOCIATED WITH CONGENITAL ATRESIA OF THE BILE DUCTS\*

(REPORT OF A CASE)

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CHOLEDOCHUS CYST is a rare anomaly of the biliary tract, approximately 180 authentic cases having been reported to date. The literature has been thoroughly reviewed in recent years by Smith,<sup>7</sup> Shallow, Eger and Waggoner<sup>6</sup> and McLaughlin.<sup>4</sup>

Many authors have advanced theories to explain the etiology of this condition. The simplest and most widely accepted is that of Yotuyanagi<sup>9</sup> who considers these cysts to be congenital anomalies due to maldevelopment of the biliary tube in the eighth week of fetal life. At this stage the common duct recanalizes from a solid cord of epithelial cells, and abnormalities may lead to atresia or cystic areas. Such a theory places the etiology of this condition on the same basis as that suggested by Bremer<sup>1</sup> for duplication of the bowel. In the latter condition areas of atresia and cysts are sometimes present in the same intestine.<sup>5</sup>

It is rather surprising that co-existing choledochus cyst and bile duct atresia has not been reported previously, but a search of the literature fails to reveal such a case. In several instances obliteration of the common bile duct below the cyst has been present. In none of these was there any reason to believe the obstruction a congenital atresia since in all cases there was a prolonged period during which the patient was free from jaundice. Shallow, Eger and Waggoner<sup>6</sup> consider these to be cases of congenital stenosis with subsequent inflammatory obliteration of the duct.

The following case is believed to be unique in that a cyst of the common bile duct was associated with congenital atresia of both hepatic and common bile ducts.

## CASE REPORT

L. J., a female infant age 4 months, was admitted to the Royal Victoria Hospital April 14, 1948. The mother stated that the child had been jaundiced since birth and that she had passed white stools from the first bowel movement. There had been some variation in the intensity of the jaundice from day to day.

On admission the child was afebrile. There was moderate icterus of the skin and sclerae but the baby was in good condition and well nourished. Physical examination showed the liver to be moderately enlarged, but no other abdominal masses could be

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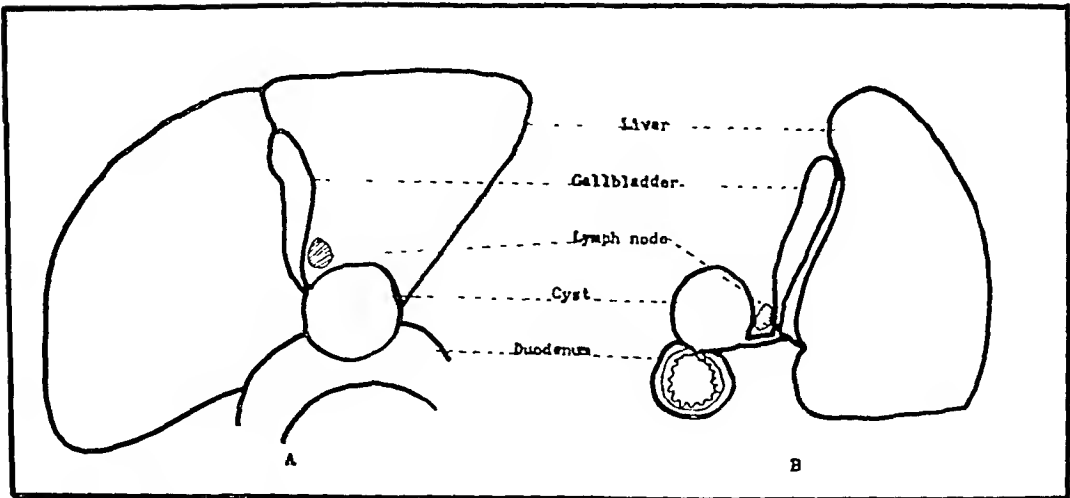


FIG. 1.—Diagram of findings at operation.



FIG. 2.—Photograph of specimen.

palpated. Laboratory investigation revealed the following data:

1. Father, mother and child were all blood group O, Rh positive.
2. Blood Wassermann negative.
3. The urine consistently contained bile and the faeces showed traces of urobilinogen and bilirubin.
4. Blood chemistry—

NPN	24.7 mg. %
Total protein	5.71 Gm. %
Albumen	4.1 Gm. %
Globulin	1.61 Gm. %
Alkaline phosphatase	50.4 units
Bilirubin—Direct	5.7
Indirect	7.6
D/I	75%
Cephalin cholesterol	Negative
Thymol turbidity	1.4
Thymol flocculation	Negative

5. Haemogram normal. Prothrombin time 20 sec. (100% of normal).

These findings were interpreted as indicating an extrahepatic obstructive jaundice and the differential diagnoses considered were, congenital atresia of the bile ducts, obstruction of the common duct due to inspissated mucus, and choledochus cyst. Laparotomy was performed May 1, 1948, under intratracheal ether anesthesia (Fig. 1). On opening the abdomen the liver presented into the wound. It was markedly enlarged and green in colour. A gallbladder was present, and aspiration of it yielded colorless mucus and no bile. The peritoneum overlying the common duct was divided and a cyst-like swelling 2 cm. in diameter was seen replacing the lower end of the duct. Aspiration of this again showed mucus but no bile. Saline was injected into the gallbladder and this caused filling of the cyst. Further dissection revealed a normal cystic duct communicating with the common bile duct just above the cyst but the common hepatic duct was represented by a fibrous cord with no lumen (Fig. 2). The cyst was removed to obtain better exposure and in doing so the duodenum was inadvertently opened, making it impossible

FIG. 3

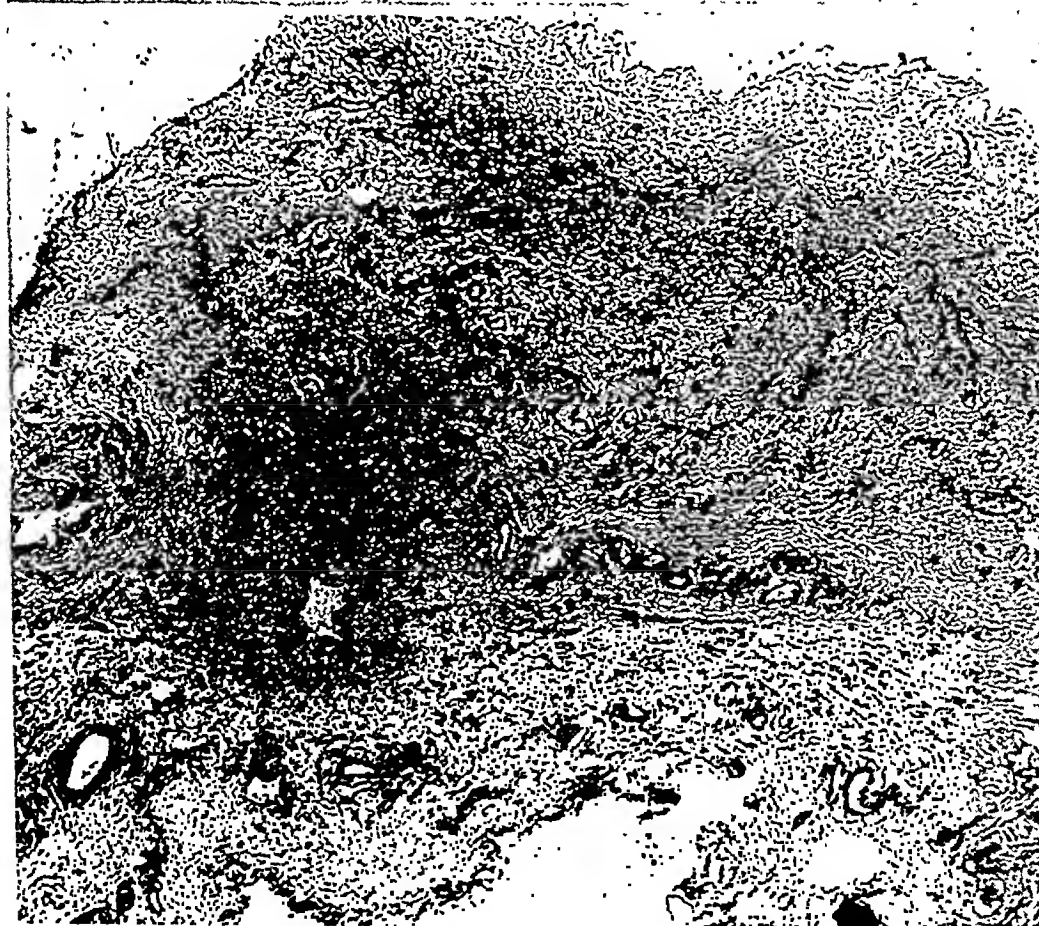
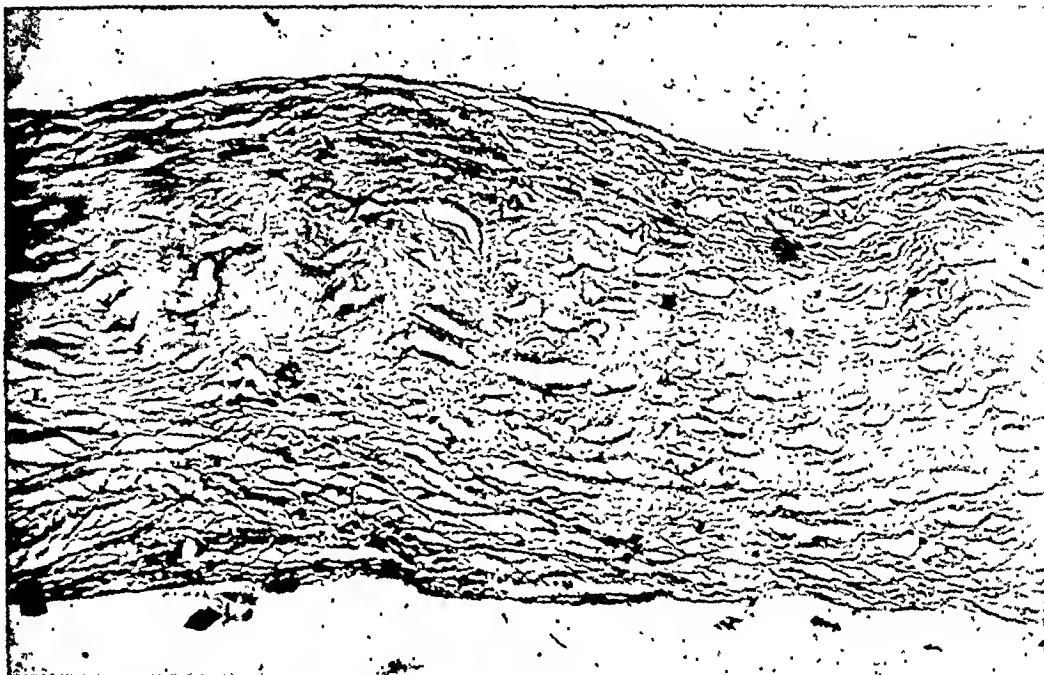


FIG. 4

FIG. 3.—Section through cyst wall showing laminated fibrous tissue and no epithelium.

FIG. 4.—Section through common bile duct with no evidence of lumen.



to demonstrate whether or not a communication had previously existed between it and the cyst. An attempt was made to obtain bile by aspiration of the atretic hepatic ducts but this was unsuccessful. The condition was considered to be inoperable. The cyst and gallbladder were removed and the abdomen was closed. The postoperative course was complicated by peritonitis, and the child died two weeks after laparotomy. Autopsy revealed that the intra-hepatic bile ducts were not completely atretic, but their walls were thickened and their lumens very small in diameter (Fig. 5).

*Pathologic Report.* (Dr. T. R. Waugh). The specimen consists of a gallbladder

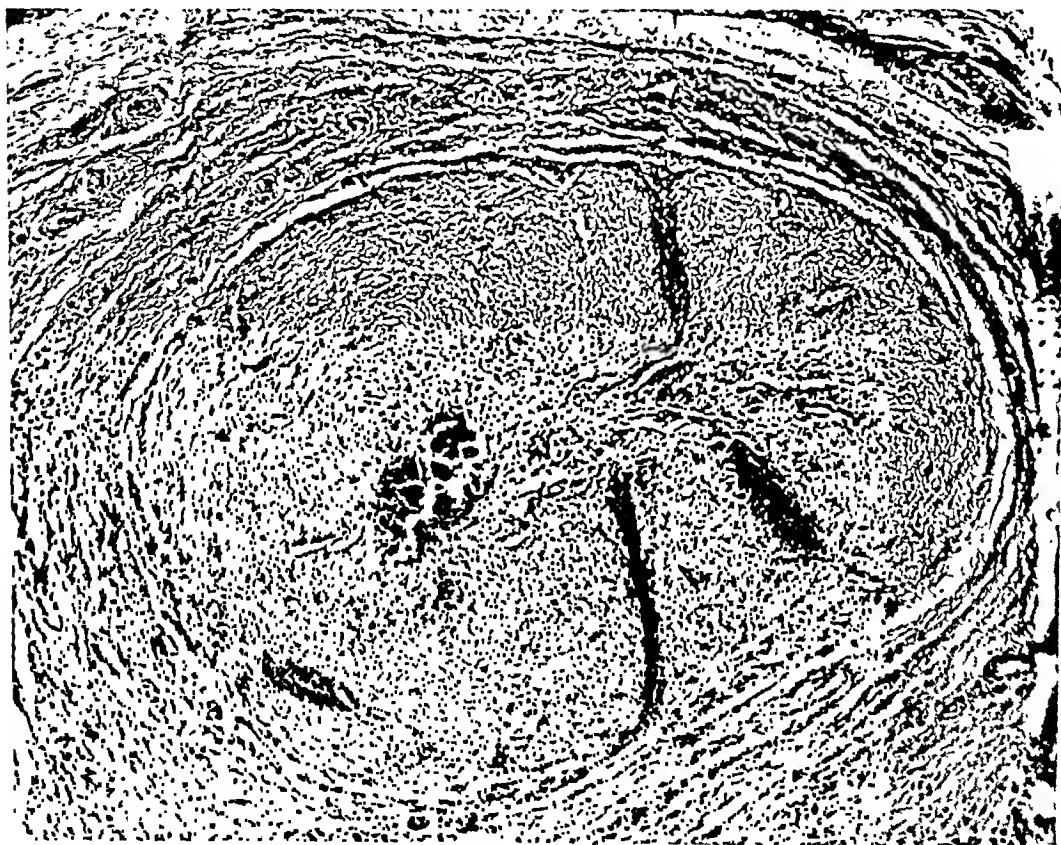


FIG. 5.—Section through the common hepatic duct. The lumen is small and contains bile. The wall is thickened and hypertrophied.

5 cm. in length terminating in a narrow cystic duct which passes into a short segment of common duct 1.8 cm. in length. The serosal surface is pearly gray, smooth and glistening and covered with a few fibrous tags. The lumen of the gallbladder is patent and empty. Both hepatic and common ducts are without lumens consisting of flattened tough fibrous tissue.

There is also a detached roughly spherical unilocular cyst 1.8 cm. in diameter. The wall is thin, white, smooth and fibrous.

Microscopic examination of the gallbladder shows the mucosa intact. Numerous Rokitansky-Aschoff sinuses are present and the muscularis is thick with occasional foci of lymphocytes in the lamina propria.

Sections of the cyst show it to consist of dense fibrous connective tissue arranged as parallel collagenous strands (Fig. 3). The inner surface lacks an epithelial lining.

## CHOLEDOCHUS CYST

Sections from the distal portion of the specimen reveal no evidence of a lumen in either the hepatic or common bile ducts (Fig. 4).

*Diagnosis.* Simple cyst—common bile duct.

Atresia of hepatic and common bile ducts.

### SUMMARY

1. A case of choledochus cyst associated with congenital atresia of the bile ducts is reported.

This is believed to be the first time that such a finding has been recorded in the literature.

2. The coincidence indicates that the etiology of both conditions may be due to abnormalities in the development of the bile ducts during recanalization of the solid stage which occurs in the 8th week of fetal life.

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# TRAUMATIC RUPTURE OF THE CHOLEDOCHUS, ASSOCIATED WITH AN ACUTE HEMORRHAGIC PANCREATITIS AND A BILE PERITONITIS\*

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TRAUMATIC RUPTURE OF THE COMMON BILE DUCT occurs very infrequently and is usually fatal because of concomittant injuries to the liver, pancreas, spleen and the intestinal tract. Invariably liberation of the bile into the peritoneal cavity results in a biliary peritonitis, with its attendant distention, toxicity, and malnutrition. The accumulated biliary ascites increases the intra-abdominal pressure, elevates the diaphragm, and inhibits the use of the abdominal muscles, so that the process of respiration is very inadequate and thereby conducive to a serious state of generalized anoxia. These altered physiologic conditions portend an unfavorable prognosis unless they can be corrected by surgical intervention.

## ETIOLOGY

Traumatic rupture of the extrahepatic biliary system is usually produced by direct force. It may be of a penetrative nature as incurred in gun shot wounds, or compressive as encountered in crushing injuries. Violent compression of the anterior abdominal wall against the lumbar vertebrae may lacerate or cause an avulsion of the common bile duct.

*Case History.*—H. G., a white boy, 7 years of age, entered the Latter Day Saints Hospital on May 6, 1947, because of an intense jaundice associated with distention, persistent vomiting, dehydration, and anoxia. The week before he had received a compressive injury to his abdomen, when a tractor crushed him against a manure spreader. The "hitch" on the tractor had struck him above and to the right of the umbilicus, forcing the impinged viscera against the vertebrae.

He was taken to a local hospital where he was treated for mild shock and then dismissed. Four days later he was readmitted to this hospital because of an intense paraumbilical pain which radiated to the right shoulder. Nausea, vomiting, dehydration and jaundice progressively increased during the next 72 hours, his condition became so serious that he was transferred to the Latter Day Saints Hospital.

The boy's acute illness was evidenced by a temperature of 104.8 F., a respiratory rate of 62, and a pulse rate of 186. His abdomen was so distended that breathing was most laborious and superficial. A bilateral pleural effusion, abdominal ascites, jaundice, and an intense acidosis added to the gravity of his condition.

Emergency treatment consisted of oxygen therapy, gastric decompression, and the intravenous administration of electrolytes, protein hydrolysates, whole blood, and blood plasma. Continuous penicillin therapy was instituted. An abdominal paracentesis recovered 3,000 cc. of a clear golden-colored bile, cultures of which were negative for bacterial

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contamination. Laboratory studies resulted in the following data: 2,800,000 RBC, 64 per cent hemoglobin, 18,200 WBC, with a differential polymorphonuclear count of 88 per cent. The icteric index was 76. The urine contained 4 plus bile, 3 plus acetone bodies, and 2 plus albumin. The stools were acholic. The prothrombin time was 46 seconds. The total plasma proteins were 4.8 Gm.; serum globulin 1.8 Gm.; serum albumin 3 Gm.

After 4 days of intensive preoperative preparation the abdomen was opened under a balanced anesthesia consisting of cyclopropane and curare. Twenty-three hundred cubic

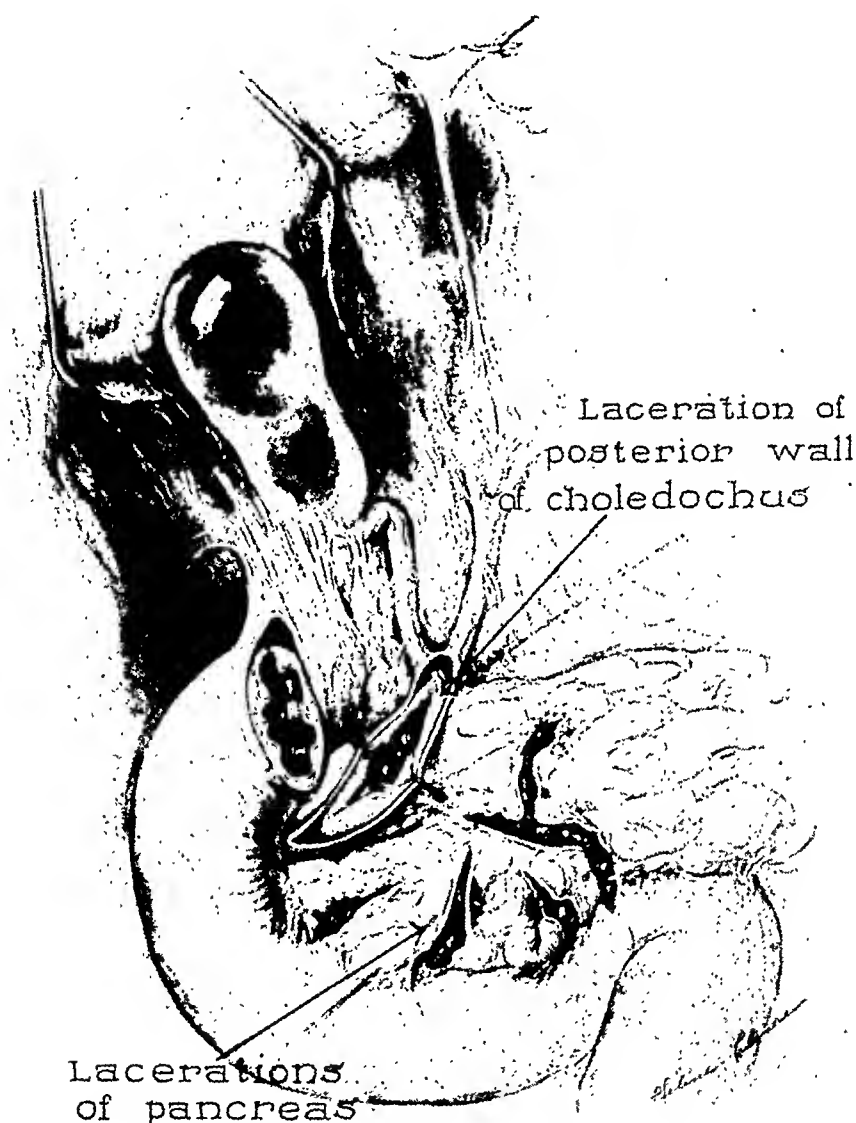


FIG. 1.—A drawing showing conditions found at the time of operation. The traumatic laceration of the posteromedial wall of the choledochus was situated so the bile could drain into the lesser omental sac. Note the multiple lacerations of the pancreas.

centimeters of normal-appearing bile was aspirated from the abdominal cavity. The stomach and colon were elevated and pushed forward by a large fluctuating mass. The tumefaction proved to be 2100 cc. of bile, which had become loculated within the lesser omental cavity. There was no gross evidence of injury to the liver and both the gallbladder and cystic duct were collapsed, but otherwise normal.

How had the bile gained access to the peritoneal cavity? In order to answer this question 50 cc. of a solution of 70 per cent diodrast was injected into the collapsed gallbladder, and a visualizing cholangiogram was taken. The gallbladder, cystic duct, common

hepatic duct, and the upper segment of the choledochus were clearly visualized. None of the contrast medium was able to pass through the ampulla of Vater, indicating that the edematous pancreas had produced a compressive occlusion of the ampullary orifice. In the upper third of the choledochus a small stream of diodrast was seen to penetrate the ductal wall and escape into the lesser omental cavity. The extravasated diodrast localized the laceration as being on the posteromedial wall of the common bile duct. (Fig. 1).



FIG. 2.—A postoperative cholangiogram obtained by injecting 54 cc. of solution of 70 per cent diodrast into the cholecystostomy tube. Note that gallbladder, cystic duct, common hepatic duct, and proximal portion of the choledochus are well visualized. The contrast medium, however, was unable to pass through the ampulla of Vater because of concentric compression of the edematous and traumatized pancreas.

These operative cholangiograms presented several important findings: (1) The laceration was situated on the posteromedial wall of the common bile duct so that the bile escaped into the lesser omental cavity; (2) a traumatic pancreatitis had further com-

## RUPTURE OF THE CHOLEDOCHUS

plicated the problem by effecting a complete occlusion of the ampulla of Vater; and (3) the gallbladder and cystic duct were both patent and could be used to decompress the common hepatic bile duct while the obstructive pancreatitis was subsiding. A decompressive cholecystostomy was accomplished by inserting a large rubber catheter into the gallbladder and bringing it out through a stab wound. A large Penrose drain was placed in the foramen of Winslow so as to drain the bile from the lesser omental bursa. No attempt was made to suture the traumatized choledochus.



FIG. 3.—A postoperative cholangiogram made several days later. Observe that the contrast medium now flows into the duodenum, and that the gallbladder, cystic duct, and choledochus are no longer dilated. The pancreatitis has not completely subsided for the "thread like pattern" indicates a narrowing of the ampullary segment of the common bile duct.

Supportive therapy consisted of the administration of whole blood, blood plasma, protein hydrolysates, vitamins and electrolytes in sufficient quantities to maintain a positive balance. On the fifth postoperative day an additional 1,500 cc. of bile was removed from the peritoneal cavity by an abdominal paracentesis, in spite of the fact that there had been a copious flow of bile from the cholecystostomy tube. A postoperative

cholangiogram was obtained by introducing 54 cc. of diodrast into the gallbladder, through the cholecystostomy tube. The entire extrahepatic biliary system was clearly visualized. Apparently the rent of the common bile duct had completely healed for none of the diodrast escaped into the lesser omental cavity. The ampulla of Vater, nevertheless, was still obstructed, indicating the necessity for continued decompression. (Fig. 2)

One week later, another series of cholangiograms were made and they demonstrated a complete functional recovery of the choledochus. The laceration had been repaired and the obstructive pancreatitis had subsided sufficiently to permit the diodrast to pass down the common bile duct into the duodenum (Fig. 3). There was no further need for decompression of the common bile duct hence the drainage tube was removed. Ten months have elapsed since the injury and his recovery has been most pleasing as evidenced by a gain of 15 pounds in weight.

#### DISCUSSION

Spontaneous or traumatic rupture of the extrahepatic biliary system invariably results in a troublesome bile peritonitis. The bile salts and acids evoke a mild inflammatory irritation of the peritoneum and omentum, but unless there is a concomittant bacterial infection the inflammatory reactions are minimal. It was interesting to note that 8,900 cc. of bile was removed from this youngster's peritoneal cavity but no inflammatory exudate was encountered at the primary operation. The appearance of jaundice usually coincides with the onset of toxic symptoms. According to Harkins, Harmon and Judkins,<sup>2</sup> a secondary bacterial infection can and does enhance the toxicity of the biliary peritonitis.

This case demonstrates the fact that lacerations of the choledochal wall will heal spontaneously if the intraductal pressure can be maintained at a low level by continuous decompression. This is verified by the rapidity with which the choledochus heals after drainage tubes are removed. It is imperative, however, that the external decompression be maintained until there has been a complete reparation of the ductal wall, and until the patency of the ampulla of Vater had been confirmed.<sup>3</sup> Such information can be obtained by serial cholangiographic studies.

It is a common belief that if pancreatic ferments are activated by bile salts, autodigestion of surrounding tissues occurs. It is significant, however, that this patient had multiple lacerations of the pancreas, which were severe enough to produce hemorrhagic changes within the pancreas itself, yet there were no signs of tissue digestion around the pancreas, in spite of the presence of extravasated bile. Careful examination failed to show any evidence of saponification of adipose tissues. Apparently this fermentative autolysis occurs only when dead or devitalized tissues are present, as normal tissues are able to withstand the digestive actions of these combined ferments. This supposition agrees with the observations of Dragstedt, Haymond, and Ellis.<sup>1</sup>

#### SUMMARY

1. Traumatic rupture of the common bile duct may be produced by injuries that are either penetrating or compressive in nature.
2. A bile peritonitis results from the extravasation of bile into the peri-

toneal cavity. A total of 8,900 cc. of bile was aspirated from the abdominal cavity of a seven-year-old boy, as described in this paper.

3. Lacerations or rents of the extrahepatic biliary system can be quickly and accurately localized by means of operative cholangiograms. These "radio-graphic blueprints" provide the surgeon with an accurate visual pattern of the reconstructive problem which confronts him.

4. A case is presented wherein a traumatic rupture of the postero-medial wall of the common bile duct occurred, permitting the extravasation of bile into the lesser and greater peritoneal cavities. The bile peritonitis was aggravated by a concomittant acute pancreatitis which completely occluded the ampulla of Vater, thereby compelling all the bile to escape through the lacerative opening.

5. This case demonstrates that lacerations of the choledochal wall will heal spontaneously providing the extrahepatic ductal system is kept decompressed by external drainage. The decompressive tubes should be left in situ until serial cholangiograms demonstrate that the ductal defect has been completely healed and that the associated pancreatitis has subsided sufficiently to permit the free passage of bile through the ampulla of Vater into the duodenum.

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# MULTIPLE CARCINOMAS OF THE STOMACH\*

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WHILE MULTIPLE MALIGNANCIES of the gastro-intestinal tract are second in frequency to skin lesions,<sup>1</sup> multiple malignant neoplasms of the stomach are comparatively rare. Warren and Gates,<sup>1</sup> in 1932, in a review of the literature, reported 25 primary multiple stomach malignancies. Brindley, Dockerty and Gray<sup>2</sup> reported 23 multiple malignancies of the stomach among 1,184 carcinomas of the stomach seen at the Mayo Clinic between 1932 and 1941, and they add an additional one with four carcinomas of the stomach. Hellendall<sup>3</sup> and Rickles<sup>4</sup> each reported one case, the latter having one with 5 individual carcinomas.

Perhaps heredity, congenital anomalies or hormonal influences play a role in multiple carcinomas.<sup>3</sup> Rhoads<sup>5</sup> states that studies in recent years provide evidence that cancer may be a local manifestation of a general disease. This may explain in part the frequency of primary multiple tumors.

Warren and Gates<sup>1</sup> noted that multiple cancers occur at approximately the same age as single ones and that they occur more frequently than can be explained on chance alone. They make use of the following criteria in evaluating multiplicity:

1. Each of the tumors must present a definite picture of malignancy.
2. Each must be distinct and the probability of one being a metastasis of the other eliminated.

They also feel that as long as the tumors are clearly independent, their location relative to one another is immaterial. In their series of 1,078 cancer autopsies, the frequency of primary multiple tumors was 3.7 per cent, whereas on the basis of all statistics, the frequency is 1.84 per cent of cancer cases. (The question of immunity or a predisposition to multiple tumors is still debatable.)

The occurrence of three cases with primary multiple carcinomas of the stomach from 1943-1947 in one institution is rare indeed, and hence we are presenting these cases.

## CASE REPORTS

Case 1.—H. M., a 46-year-old white male, was seen May 19, 1947, and stated that he had been treated for about 15 years for anemia. About one year ago, began having pain in the left upper quadrant; 7 months history of loss of appetite; 10 days ago had a vomiting spell with coffee-ground material present. Weight loss 30 lbs.

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# CARCINOMA OF STOMACH

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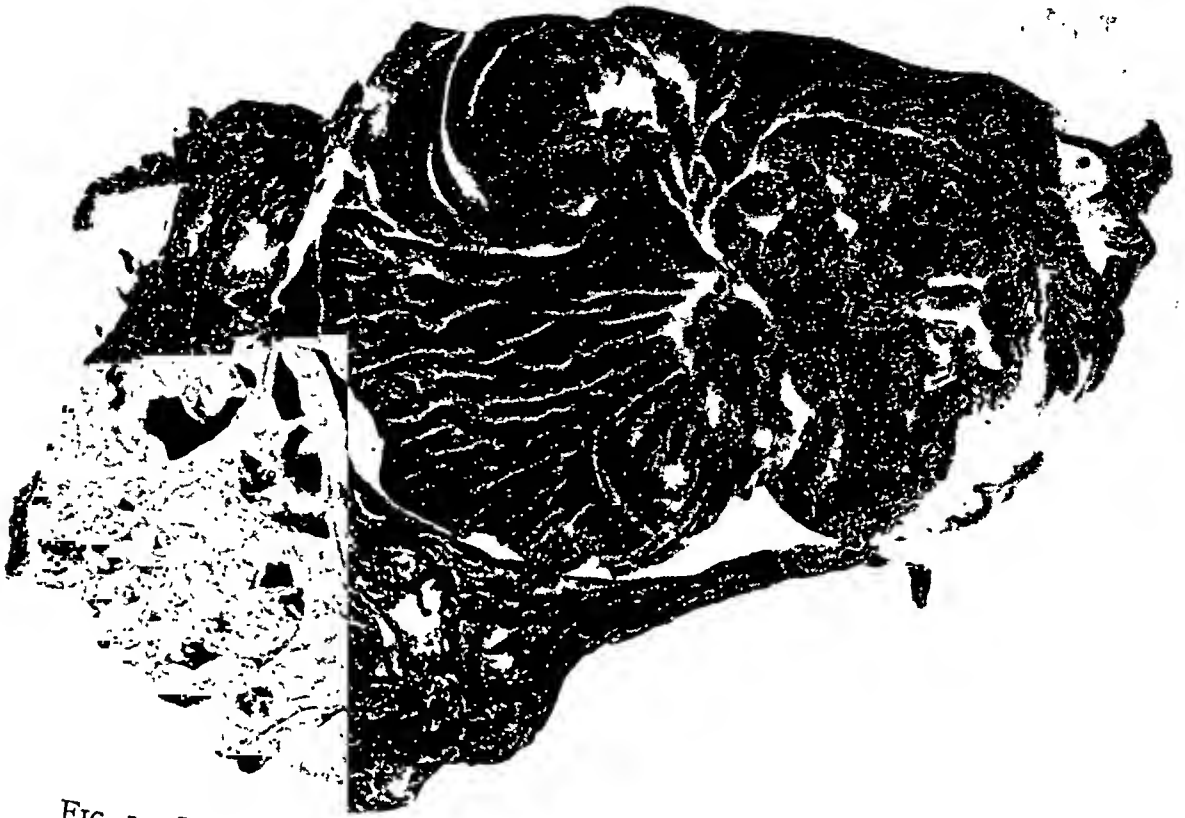


FIG. 1.—Two lesions measuring 9 cm. and 4 cm. invading muscle.

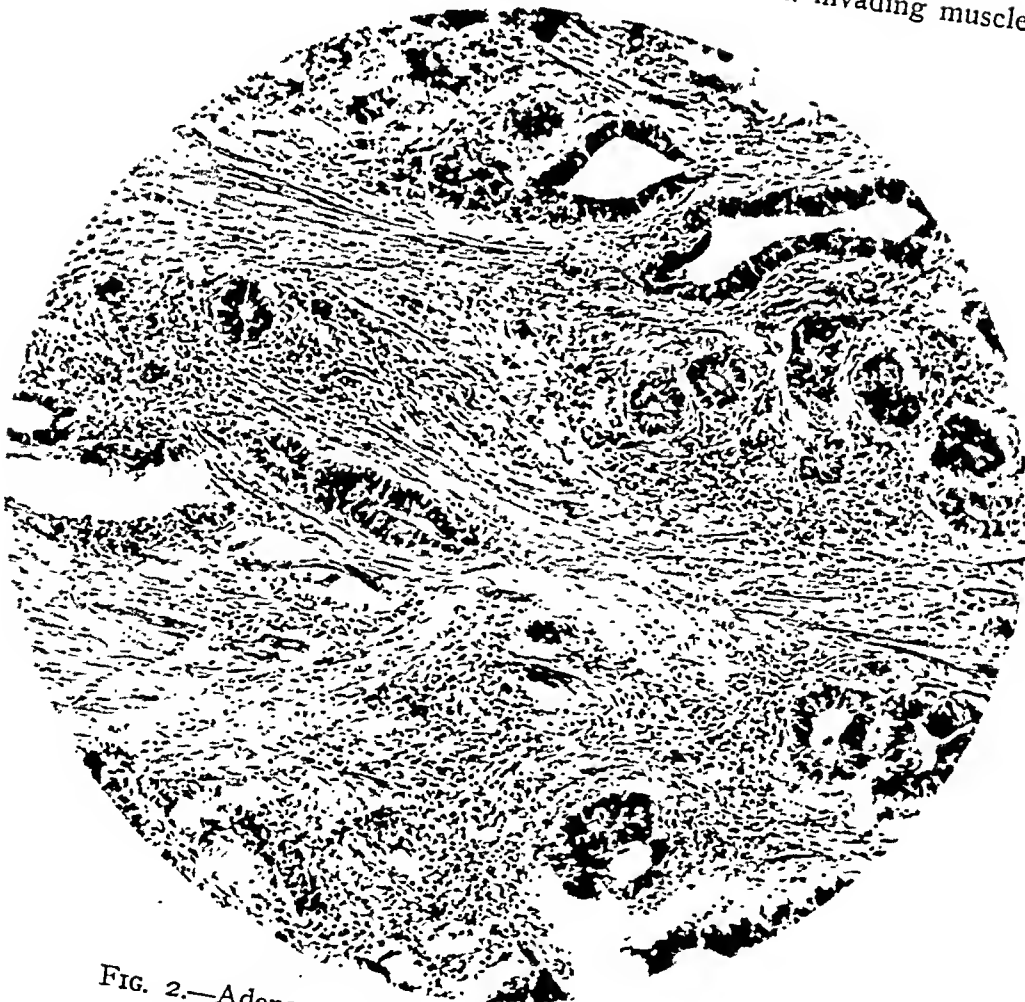


FIG. 2.—Adenocarcinoma invading the musculature.

Had roentgenograms elsewhere, June 1946, which were apparently negative. Had repeat roentgenograms, January 1947, when a large, ulcerating lesion was noted in the pre-pyloric region of the stomach with surrounding filling defect and fixation. Diagnosis of a massive, ulcerating carcinoma with obstruction was made. Gastro-intestinal series done here on admission showed a spastic esophagus in the lower end with some hesitation, but with no definite evidence of tumefaction. The 24-hour films showed 60 per cent residue in the stomach. Films also confirmed impression of previous films, namely, that a gastric carcinoma was present.

*Physical examination.* A pale-looking, thin male in no acute distress. No tumefactions noted anywhere. Abdominal examination negative. No Blummer's shelf. Wassermann negative.

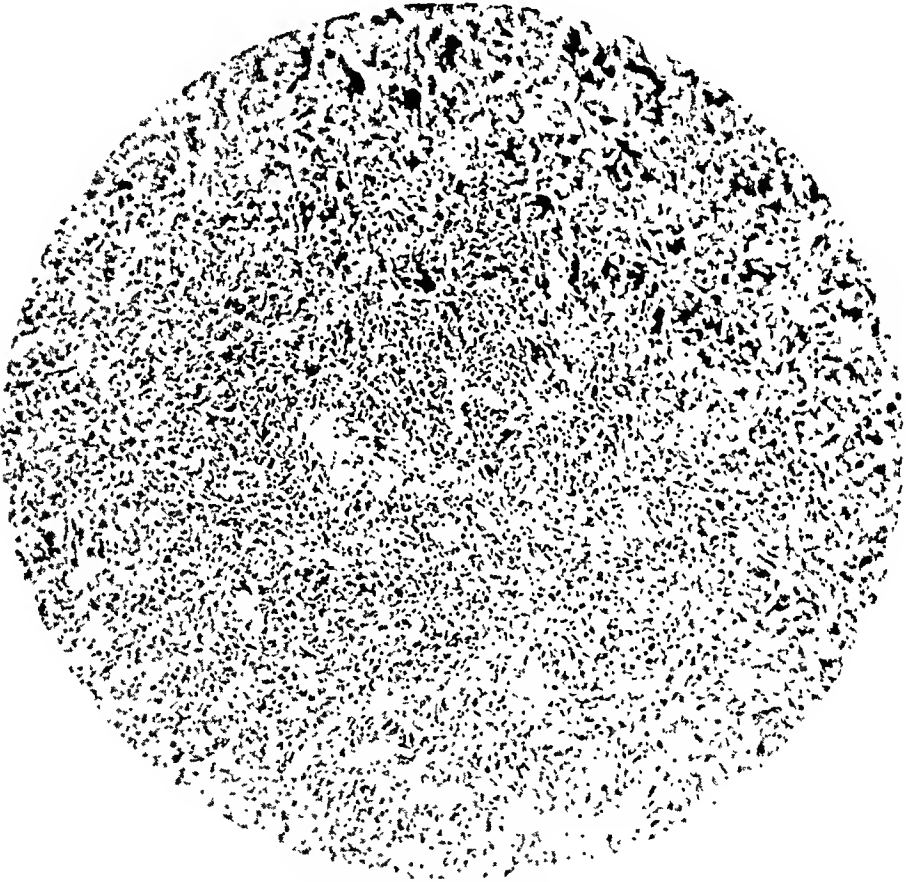


FIG. 3.—Anaplastic carcinoma with diffuse infiltration.

*Laboratory data:*

Hemoglobin: 65 per cent (9.08 Gm.)

RBC: 3,140,000

WBC: 9,250

Alb.: 3.66; globulin: 2.58

NPN, sugar and chlorides within normal limits.

Patient was placed on our usual high caloric, high protein, high vitamin diet and prepared for two weeks with blood transfusions and diet until his hemoglobin was 75 per cent; red blood count 3,800,000; hematocrit 47 per cent; and he had gained weight.

## CARCINOMA OF STOMACH

The plasma proteins did not rise. In view of the low blood volumes in patients with gastro-intestinal cancer and the persistent hypoproteinemia in spite of increased caloric and protein intake, our main concern was to treat the anemia preoperatively. We felt that the two-week nutritional preparation and the hemoglobin of 75 per cent was sufficient to allow us to operate with safety.

The patient was operated on and multiple carcinomas of the stomach were found. One involved the cardia and the other, the pre-pyloric region.

*Gross.* Stomach specimen shows a cardiac lesion 9 cm. in diameter. (1) The center of the growth showed ulceration with irregular, raised proliferation in the periphery. The tumor was fairly firm and invaded the muscular coat. About 2½ cm. from this growth, another tumor measuring 4 cm. in diameter (2) was found that invaded the muscular wall.



FIG. 4.—Two lesions measuring 9 cm. and 3 cm. infiltrating the musculature.

*Microscopic:* (1) Sections show an adenocarcinoma invading the musculature of the stomach. Gland formation is prominent.

(2) Sections show a diffuse infiltration of the stomach by a carcinoma. The growth is anaplastic in character and does not show gland formation.

*Operation:* A total gastrectomy was done via the abdominal route. Patient received 1000 cc. of blood in the operating room.

*Postoperative Course:* Uneventful. Patient was discharged in 14 days. At no time did he experience symptoms suggestive of the dumping syndrome. He is now, June, 1948, on a bland diet routine taken in 5 feedings. He is gaining weight and working.

**Case 2.**—T. N. Patient was seen here September, 1945, with a history of abdominal

pain for 8 months, loss of appetite for one week, loss of 28 lbs. in a year, weakness 4 to 5 months. Patient stated that for the past 5 months he has had constant epigastric pain, occasionally relieved by the ingestion of food. He also stated that he was treated in 1943 for a gastric ulcer, but at no time did he have roentgen-ray studies.

Physical examination revealed a 64-year-old white male in no acute distress. Abdominal examination: Liver, spleen, and kidneys not palpable. There was definite tenderness in the epigastric region, but no tumefactions were noted. Rectal examination was essentially negative.

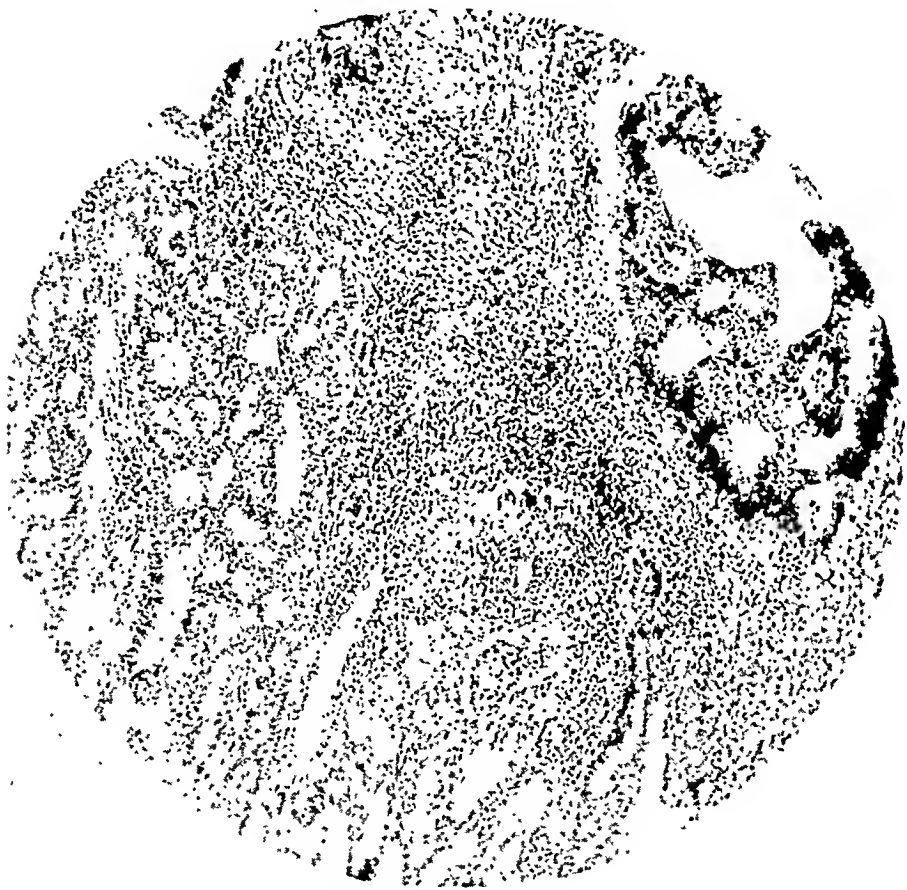


FIG. 5.—Infiltrating adenocarcinoma.

*Roentgenograms:* Fluoroscopic examination revealed a normal esophagus. The stomach was slightly large, modified fish-hook in type and low in position. Fluoroscopy and roentgen-ray films revealed a constant filling defect on the lesser curvature of the body of the stomach near the cardia. Peristalsis was normal; emptying began immediately and the cap was normal. The 3-hour film showed the stomach to be empty. Impression was that of an advanced carcinoma of the stomach.

*Gastroscopic examination:* The antrum and angulus were seen and showed no evidence of pathology. Peristalsis was very active. On the lesser curvature, in the body of the stomach, could be seen a large, ulcerating lesion, the edges of which were raised. The picture was typical of carcinoma of the stomach.

Patient was admitted to the hospital November 2, 1945, for a gastric resection.

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### *Laboratory data:*

Hemoglobin: 96% (13.8 Gms.)

RBC: 5,080,000

WBC: 9,450

Hematocrit 45%

Gastric analysis was negative for HCl in all samples with faint trace of blood.

Blood sugar 107 mg.%, NPN 43, Chlorides 435.

Patient was prepared in the usual manner with transfusions and diet and on November 11, 1945, a subtotal gastric resection was done. Two distinct areas of malignant degeneration were noted; one in the body of the stomach near the cardia and the other in the

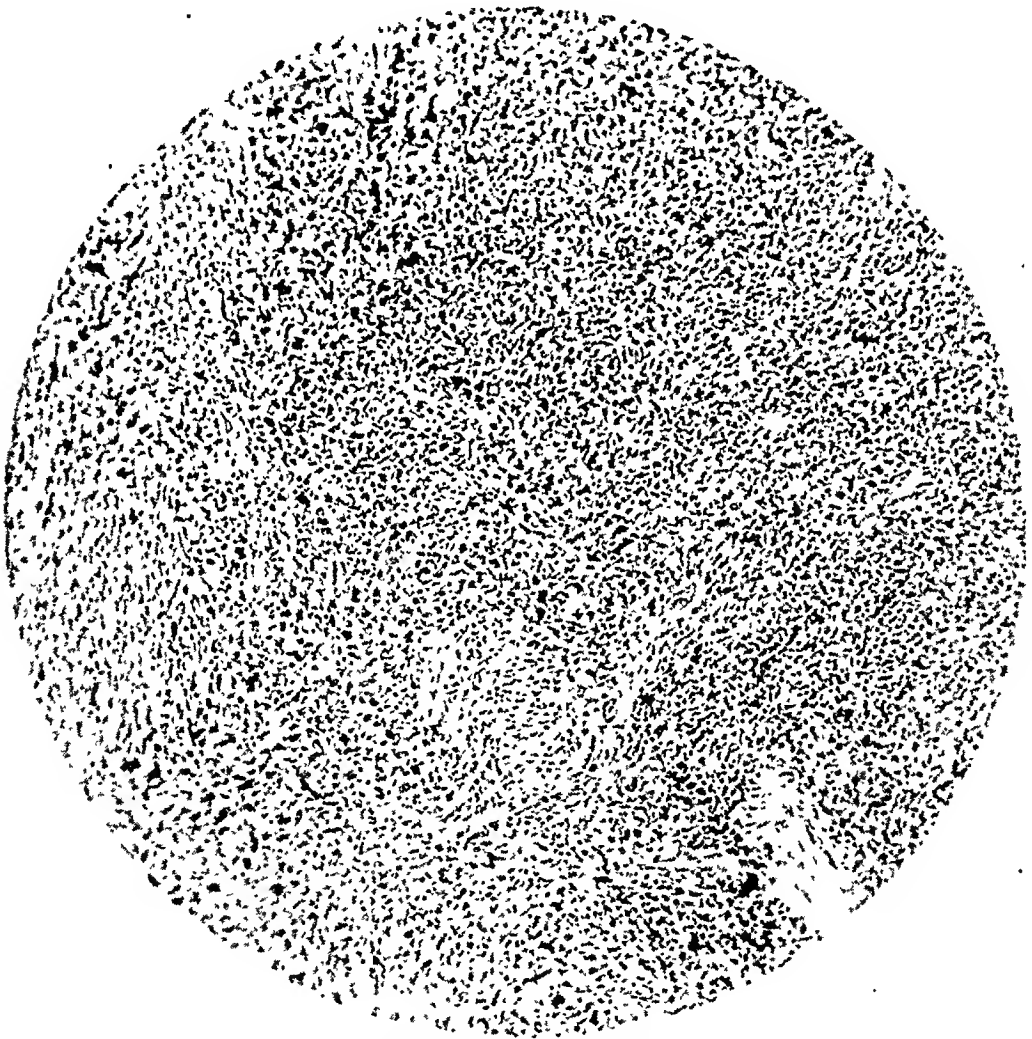


FIG. 6.—Anaplastic infiltrative carcinoma.

antrum. Regional malignant lymphatic spread was noted along the course of the left and right gastric arteries necessitating almost complete resection of the stomach.

*Gross.* Specimen from the stomach showed two distinct tumors. The larger one at the cardiac end measured 9 cms. in diameter. (3) There was central ulceration with irregular papillary proliferations in the periphery. The tumor was soft in consistency and reddish in coloration. The second lesion measured about 3 cms. in diameter. (4) It was papillary in type and reddish in coloration. Both tumors were found to infiltrate the gastric musculature.

*Microscopic.* (3) Sections show an infiltrating adenocarcinoma. (4) Sections show an anaplastic infiltrative carcinoma.

Patient's postoperative course was uneventful and he was discharged November 21st. Has been seen at 3-month intervals since then and a gastrointestinal series done March 25th revealed no evidence of recurrence. Patient was last seen September, 1946, at which time he complained of symptoms typical of the dumping syndrome. There was no intra-abdominal evidence of recurrent tumefaction. No evidence of obstruction. Rectal examination was also negative. A questionnaire reply, May, 1948, stated that patient had died of bronchopneumonia.

**Case 3.—J. R. K.** Patient was a 64-year-old white female, admitted in January, 1943. She was a gravida 2 and had her menopause at 46. Had a bloody vaginal discharge one



FIG 7—Two lesions measuring 10 x 6 cm and 4 x 6 cm with invasion of the musculature

year ago. Pelvic examination revealed a badly lacerated cervix. Induration was present on the anterior lip. Some erosion and ulceration in the canal. Biopsy proved to be epithelioma of the cervix. Patient was then treated in the usual manner with radium and x-radiation therapy. Her gastro-intestinal history was negative on admission. Patient was seen at regular intervals and as far as the cervical carcinoma was concerned, there was no recurrence after treatment.

On July 31, 1946, during a routine hospital visit, patient stated that for the past 5 weeks she had noticed a mass with some tenderness in the lower mid-abdomen. Had also complained of nausea and vomiting. She had lost weight, but stated that her appetite had



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been poor. There was no pain in the epigastrium. No change in her bowel habits, no bloody or tarry stools.

Physical examination revealed a freely movable mass just beneath the umbilicus. This mass was not attached to the uterus and was markedly tender on deep palpation.

Sigmoidoscopic examination was negative for tumefaction. Patient had a gastrointestinal series August 5, 1946. Fluoroscopic examination revealed that the esophagus was normal, the stomach was large, with a constant filling defect on the greater curvature in the body. The cap was normal. The six-hour film showed a small amount of residue. On the 24-hour film, the stomach was empty. Diagnosis of carcinoma of the body of the stomach, moderately advanced, with no evidence of obstruction, was made. Chest roentgenograms were negative.

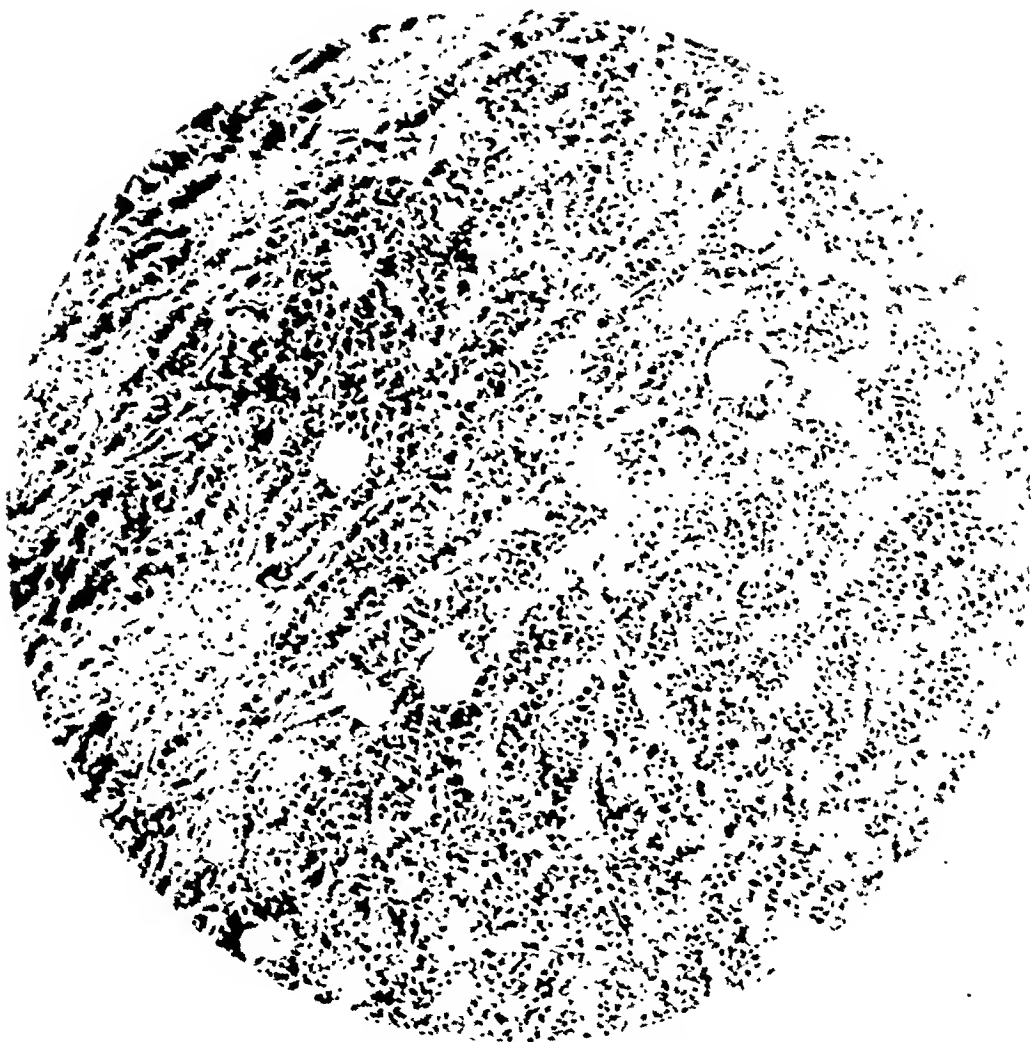


FIG. 8.—Anaplastic carcinoma with marked infiltration of stomach wall.

Patient was admitted to the hospital for gastric resection on August 9, 1946.  
*Laboratory data:*

Hemoglobin 81% (11.6 Gm.)  
RBC: 4,280,000  
NPN 30; Glucose 107; Albumin 3.26  
Globulin 2.23; Chlorides 571 mg. %  
Urine negative, except for 1 plus albumin.

Patient was prepared with diet and transfusions in the usual manner and on August 20, 1946, a subtotal gastric resection with a resection of the transverse colon was done.



Findings at operation were as follows: There was no liver metastasis, but there was considerable fixation of the tumor mass involving the lower third of the stomach and transverse portion of the colon. Several nodes were found in the great omentum.

*Gross.* Specimen from the stomach showed the presence of two separate lesions. The larger one measured 10 x 6 cms.<sup>5</sup> The growth was fairly firm in consistency, white in coloration and showed ulceration. The smaller lesion measured 4 x 5 cms.<sup>6</sup> The tumor was soft in consistency and showed papillary projections. Both tumors invaded the muscular coats.

*Microscopic.* <sup>5</sup> and <sup>6</sup> Both tumors show carcinoma. The tumor cells are anaplastic and show marked infiltration of stomach wall.



FIG. 9.—Anaplastic carcinoma with marked infiltration of stomach wall.

Patient's postoperative course was uneventful until about August 26, when she began to develop signs of obstruction. She was treated symptomatically and on September 10, an exploratory laparotomy was done. A walled-off abscess in the region of the duodenum was found. Drain was inserted.

On September 12, patient suddenly went into coma and ceased breathing. Autopsy revealed congestion and edema of the lungs, peritonitis, cystitis and ulceration of the bladder, adenoma of thyroid and leiomyomatous polyp of cervix.

*Conclusion.* We have presented three cases of multiple primary carcinomas of the stomach. At no time was it possible clinically, radiologically or gastroscopically to make the preoperative diagnosis as to the multiplicity of the tumefactions.

## CARCINOMA OF STOMACH

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# INTERNAL HERNIA BEHIND THE JEJUNAL LOOP OF A POSTERIOR GASTRO-ENTEROSTOMY\*

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AN UNUSUAL TYPE OF INTERNAL HERNIA was recently encountered on the Surgical Service of the Presbyterian Hospital, and since records of similar cases are rare in the American literature it is being reported in this paper.

## CASE REPORT

F. V. Unit Number 644916. *Chief Complaint.* On February 29, 1948, a 48-year-old married German carpenter entered the hospital for the second time complaining of crampy, lower abdominal pain of 24 hours duration.

*Previous Admission.* He was first admitted to the Presbyterian Hospital approximately 7 years ago for treatment of a stenosing duodenal ulcer. He had suffered from ulcer symptoms for over 12 years and had sustained 2 major complications, the first a gross hematemesis 3 years before admission and the second, a perforation with operative repair 2½ years before admission. His symptoms were those of pyloric obstruction and a gastro-intestinal series revealed 80-90 per cent retention of the motor meal at 6 hours, with a crater in the distal portion of the duodenal bulb. For 3 weeks he was treated conservatively, but at the end of that time he still showed a 50 per cent 6 hour retention of the motor meal by roentgen-ray. In view of this coupled with the past history of both hematemesis and perforation, a partial gastrectomy was done on July 18, 1941. The duodenum was found to be densely adherent to the liver and gallbladder. An ulcer was found on the posterior duodenal wall adherent to and penetrating into the pancreas. About three-fifths of the stomach and part of the first portion of the duodenum including the ulcer were removed. A posterior, retro-colic, Polya type of gastro-enterostomy was done with the afferent limb of the jejunum being approximated to the greater curvature side of the stump of the stomach. The postoperative course was marred by broncho-pneumonia followed by empyema which responded to thoracotomy drainage. The gastro-enterostomy functioned well from the start and 5 weeks after the initial operation, he was sent home on a regular diet.

He was followed in the clinic until September 18, 1941, at which time he had no complaints, appeared well and was gaining weight. After this visit, the patient failed to return to the Surgical Follow-up Clinic.

*Present Illness.* Following the above, the patient was apparently well for the ensuing 7 years until 24 hours before admission when, one hour after breakfast, he noted the onset of severe crampy, knifelike, lower abdominal pain. This was followed by nausea and the vomiting of greenish-yellow fluid. The pain was relieved somewhat by sitting up and was made worse by lying down. During the next 24 hours, he vomited nearly all the food and liquid he attempted to eat or drink. He passed gas by rectum but had had no bowel movement in two days. There was no difficulty with micturition. His pain

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## INTERNAL HERNIA

became increasingly severe and he visited his local doctor who gave him Morphine .015 Gm. and Atropine .0006 Gm. by hypodermic and referred him to the Presbyterian Hospital where he arrived 2 hours later.

*Physical Examination.* Examination revealed an uncomfortable but drowsy male sitting on the edge of the examining table. The pulse was 72, blood pressure 110/60, respirations 16 and temperature 98.0° per rectum. The skin and tongue showed some evidence of dehydration. The heart rate was slow with occasional extrasystoles and bigeminal rhythm. The abdomen showed the scar of the previous operation and was silent. There was marked spasm of both rectus muscles, but this seemed to be largely voluntary and could be relaxed when the patient was distracted. There was some left lower quadrant tenderness and he stated that this was the most uncomfortable area. Rebound tenderness was referred to this area. No mass could be felt. On rectal examination there was some fullness anteriorly above the prostate but there was no definite mass or tenderness.

*Laboratory Data.* The white blood count was 8,600 with 72 per cent polymorphonuclear leukocytes and 28 per cent lymphocytes. The urine was negative. Four position films of the abdomen showed slight dilatation of the large bowel with gas descending to the level of the upper sigmoid but no gas beyond this point. There was no air under the diaphragm.

*Course.* The most likely admitting diagnosis appeared to be incomplete large bowel obstruction probably at the level of the sigmoid. Because the picture was definitely clouded by morphia and because neither the vital signs nor the physical findings seemed to indicate immediate operation, it was decided to admit this man to the wards for observation.

After arrival on the ward, the patient was proctoscoped to 18 cm., but no lesion was seen. The proctoscope could not be introduced beyond this point because of spasm. Following the instrumentation the patient vomited 300 cc. of fluid resembling bile.

Subsequently, the patient's symptoms abated somewhat, he dozed a great deal in a semi-sitting position and his physical findings varied. At times the abdomen was quite soft and non-tender. Occasionally the upper quadrants offered more resistance than the lower. He was placed on nothing by mouth, his stomach was lavaged, and he was given an infusion of 1500 cc. of 5 per cent dextrose in saline. Although his signs and symptoms seemed somewhat diminished, his white blood count rose to 14,000 with 86 per cent polymorphonuclear leukocytes 6 hours after admission.

On the following day, the attending doctor found the abdomen soft without distention or tenderness. The patient's complaints now centered on a point somewhat higher and to the left at about the level of the umbilicus. Although he occasionally regurgitated an ounce or so of clear, watery, non-fecal smelling material, intestinal obstruction now seemed less likely. On the other hand, the picture suggested the presence of a penetrating marginal ulcer, so he was allowed milk and amphotel by mouth.

During the day he behaved peculiarly in that he appeared to rest quietly or to doze in a semi-sitting position until examined by any of the staff. Then, as his bed was lowered, he would begin to moan and to complain bitterly of his pain. This suggested a strong functional element in the symptom complex and, indeed, on one occasion he promptly fell asleep after receiving a sterile hypodermic. Drug addiction was also suspected, but his wife denied any knowledge of this nor would the patient himself admit to any. It did not occur to us until later that the change in position incident to the abdominal examination might legitimately augment the symptoms due to the peculiar lesion present.

Laboratory studies this day revealed a white count of 12,900; hematocrit 45.6 per cent; plasma proteins 6.7 per cent; CO<sub>2</sub> 29.8 mEq/l; Cl. 101.4 mEq/l; direct Na 137.4 mEq/l; K 4.1 mEq/l; all blood chemistry values being within normal limits. A repeat erect film of the abdomen showed some increase in the gas contained within the large bowel and the findings were again reported as consistent with low grade obstruction of the left colon.

Later that day and during the night the patient's pain became more severe and steady and failed to respond to sedatives, milk or amphogel. A repeat upright film of the abdomen showed the same general appearance as before, but now there appeared, in addition, a fluid level in the stump of the stomach and some moderately dilated loops of small bowel. There was still no air under the diaphragm. He continued to vomit small amounts of clear fluid and the white count rose to 15,600 with 90 per cent polymorphonuclear leukocytes, but the pulse, temperature, respirations and blood pressure remained within normal limits. He died suddenly that night in considerable pain, 81 hours after the onset of his symptoms.

*Significant Post Mortem Findings.* Autopsy showed a moderately distended abdomen which contained approximately 2000 cc. of blood-tinged fluid. The large bowel was two to three times the normal calibre with gas extending as far as the sigmoid where the

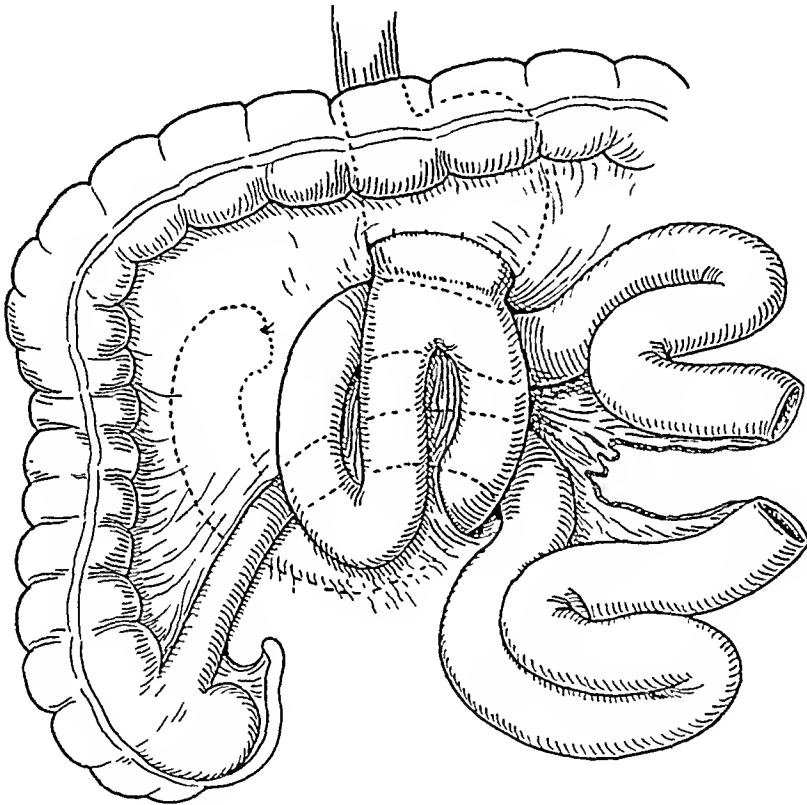


FIG. 1.—Diagrammatic sketch of the internal hernia found at autopsy. The entire small bowel from the mid jejunum to a point 15 cm. from the ileocecal valve had passed behind the jejunal loop of the posterior gastro-enterostomy from right to left. With the transverse colon reflected upward, as pictured, the hernial ring is formed by the afferent jejunal limb anteriorly, the gastro-enterostomy and transverse mesocolon superiorly, the transverse mesocolon posteriorly and the ligament of Treitz inferiorly.

lumen was uniformly constricted without any evidence of an actual organic lesion. The ascending and transverse colon and mesocolon—especially on the right near the hepatic flexure were the site of considerable edema and subserosal hemorrhage. This was found to be due to obstruction of the mesenteric veins. Almost the entire small bowel from mid jejunum to a point about 15 cm. proximal to the ileocecal valve was bluish purple in color with extensive edema and subserosal hemorrhage both in the bowel wall and in

the mesentery. This entire segment of bowel was found to have passed behind the gastro-enterostomy loop from right to left through the space formed (with the transverse colon reflected upward) by the afferent jejunal limb anteriorly, the gastro-enterostomy and the transverse mesocolon superiorly, the transverse mesocolon posteriorly and the ligament of Treitz inferiorly (Fig. 1). Although this bowel segment was occluded at its proximal and distal limits so that this, in effect, constituted a closed loop, the lumen was only slightly distended. The major disturbance seemed to be more one of venous distention and hemorrhage as a result of occlusive stretching and compression of the root of the mesentery at the hernial ring. Here, the superior mesenteric vein was markedly constricted with great engorgement peripheral to this point. Fibrinous adhesions were present between almost all juxtaposed loops of small bowel. The afferent jejunal limb was somewhat stretched, reduced in calibre and blanched. Proximal to the ligament of Treitz, the duodenum was dilated approximately twice normal size.

Microscopic sections through the involved areas showed extreme engorgement of all venous and capillary channels in all layers of the bowel wall. This was most prominent in the mucosa where every villus was swollen with congested capillaries. The submucosa was edematous and its veins were packed with red cells. The muscularis and serosa were similarly edematous and congested but to a lesser extent. There was no evidence of thrombosis or gangrene.

#### COMMENT

Although there was ample cause for ultimate death in this case, the reason for the sudden exodus is not clear. The extravasation of fluid and the extensive pooling of blood in the mesentery, together with stretching of the latter might possibly have resulted in vascular collapse. Since the heart during life was subject to abnormal rhythms, it is also conceivable that sudden cardiac arrest could have occurred through reflex mechanisms secondary to the above.

This patient should have been operated on shortly after reaching the hospital, or, at the latest, by the time the pain recurred in increased intensity and the white count rose to 15,000. The staff was misled from the start by the fact that the patient arrived at the hospital heavily sedated with morphine. It serves to emphasize once again the danger of employing morphine in the presence of an acute abdomen before the diagnosis has been made.

This case also illustrates a point which has been frequently brought out by others, namely, that in the presence of previous abdominal operations, the appearance of or increase in pain with the assumption of certain bodily positions is a warning sign which must not be ignored. If this is a persistent finding, it almost always indicates an intra-abdominal catastrophe.

#### DISCUSSION

This interesting complication of posterior gastro-enterostomy was first described by Peterson<sup>1</sup> in 1900, and is sometimes known as Peterson's hernia. In 1934, Himmelman<sup>2</sup> collected 36 cases from the literature, and in 1938, Moiroud, Salmon and Bouillon,<sup>3</sup> mentioned six additional cases apparently not included in Himmelman's series, plus one of their own. Since then, additional cases have been reported by Mayo, Stalker and Miller<sup>4</sup> and by Suiffet<sup>5</sup> making a total of 45 cases at the present writing. In the English

language, four reports may be found<sup>4, 6, 7, 8</sup> in two of which<sup>6, 8</sup> there are excellent illustrations of the abdominal viscera as found at either operation or post mortem.

In the vast majority of cases the presenting problem was one of small intestinal obstruction. In only a few was the principal pathology, as in ours, one of venous occlusion. In not all cases was there an acute incarceration or strangulation of the bowel, some cases presenting the picture of chronic low grade upper intestinal obstruction. In no case was the correct diagnosis made beforehand.

In 1934 Koch<sup>7</sup> gave the mortality for this and other types of internal hernia about a gastro-enterostomy as approximately 50 per cent. Early operative intervention is clearly of paramount importance.

Several authors<sup>2, 3, 4, etc.</sup> have suggested that, as a prophylactic measure, the afferent jejunal limb should be sutured to the transverse mesocolon in all posterior gastro-enterostomies. This measure is practical only if it can be done without angulating the afferent limb in any way that might interfere with its function.

#### SUMMARY

A case is presented and a brief discussion rendered of internal hernia behind a posterior gastro-enterostomy. With the transverse colon reflected superiorly, the hernial ring is formed anteriorly by the afferent limb of the jejunum, superiorly by the gastro-enterostomy and the transverse mesocolon, posteriorly by the transverse mesocolon and inferiorly by the ligament of Treitz.

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